Depression in People with Advanced Life-Limiting Illnesses and Extremely Short Prognoses

By

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Thesis Submitted in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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Certificate of original authorship

I, Wei Lee, declare that this thesis, is submitted in fulfilment of the requirements for the award of Doctor of Philosophy degree, in the Faculty of Health at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualifications at any other academic institution.

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Lee, W. Building your trial in cancer symptom research – starting out. Palliative Care Clinical Studies Collaborative (PaCCSC) & Cancer Symptom Trial (CST) Annual Research Forum (Panel Speaker) – Mar 2022.

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Lee, W. SKIPMDD - Subcutaneous Ketamine Infusion in Palliative Patients for Major Depressive Disorder. St Vincent's Hospital Research Week Palliative Care Seminar. Sep 2022.

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Lee, W. Depression screening, assessment, management in palliative care - Neringah Hospital. May 2023.

Media/Newsletters

Translational Cancer Research Network: TCRN PhD Spotlight Series – Dr Wei Lee. May 2019 http://www.tcrn.unsw.edu.au/news/tcrn-phd-spotlight-series-dr-wei-lee -

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Other Relevant Works/Outputs

Reviewer for eTG Complete (Therapeutic Guidelines) - Decision-making and ethical challenges in palliative care; psychological symptoms in palliative care (2021)

Reviewer for Palliative Care Bridge video series - Depression, anxiety and sleep (May 2022)

HammondCare Suicide Prevention Working Group - Developing policies to screen and assess for depression and suicidal risk in the community palliative care setting (2022-2023)

HammondCare Implementation Group for Education & Routine Screen of Psycho-existential Distress (PESAS) - Help implement routine screening and training of clinicians to respond appropriately to psycho-existential distress (2022-2023)

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Abstract

Background

Depression is a debilitating condition that affects individuals with advanced life-limiting illnesses. It can erode their physical health, sense of well-being, ability to make meaningful connections, and sense of worth when quality of life is of utmost priority. Among these individuals is a sub-group with extremely short prognoses (days to weeks), characterised by increasing frailty and dependence on others for basic care needs. The prevalence of depression and the optimal approaches to care in this population are currently unknown, and may differ from people earlier in their disease trajectories.

Aim

The aim of this project was to explore depression in people with advanced life-limiting illnesses and life expectancies of days to weeks: its assessment and diagnosis; prevalence; current, evidence-based therapies; perspectives of palliative physicians and psychiatrists in delivering care; and the feasibility of studying subcutaneous ketamine as a potentially tolerable and effective antidepressant with a rapid onset of action for this sub-group of people.

Methods

Informed by Tansella and Thornicroft's matrix, the doctoral program included two systematic reviews, one mixed-methods study (survey and focus group studies), and a phase II feasibility study (SKIPMDD).

Results

Depression affects 50% of individuals with extremely short prognoses, but randomised controlled trial evidence for any interventions is lacking. Australasian palliative physicians and psychiatrists reported screening and intervening less often for depression when prognoses are very poor. Care offered varied. Challenges were perceived in clinician training, access to interventions, linkages between services, research support, and cultural

attitudes. Better processes to integrate palliative care and psychiatric services were postulated to improve care delivery.

The project achieved the feasibility criteria set *a priori* for conducting future definitive trials ketamine's effectiveness in reducing major depressive disorder in the palliative care setting. Ultra-low ketamine dosages were well tolerated, and appeared to produce rapid-onset but transient antidepressant signals in some people.

Conclusion

Depression is prevalent in people with extremely short prognoses, but high-quality evidence to support interventions is lacking. Caring for depression is complex and challenging for palliative physicians and psychiatrists. Clinician training needs to be improved, and better care process integration between palliative care and psychiatric services would be advantageous. A future definitive trial of the use of ketamine for treating major depressive disorder in the palliative care setting may be feasible and warranted.

Abbreviations

AKPS	Australia-modified Karnofsky Performance Status
ALS	Amyotrophic Lateral Sclerosis
AMPA	Alpha-amino-3-hydroxy-5-methyl-4 isoxazoleproprionic acid
ANZSPM	Australian and New Zealand Society of Palliative Medicine
APA	American Psychiatric Association
BPRS	Brief Psychiatric Rating Scale
CADSS	Clinician Administered Dissociative States Scale
CI	Confidence Interval
CL	Consultation Liaison
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CPS	Cognitive Performance Score
DALY	Disability-adjusted life years
DRS	Depression Rating Scale (InterRAI Palliative Care)
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECOG	Eastern Cooperative Oncology Group
ECT	Electroconvulsive Therapy
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire - C30
EUC	Electrolyte Urea Creatinine
ESAS	Edmonton Symptom Assessment Scale
FBC	Full Blood Counts
FVC	Forced Vital Capacity
GRADE	Grading of Recommendations Assessment, Development and Evaluation

HADS	Hospital Anxiety and Depression Scale
HADS-D	Hospital Anxiety and Depression Scale – Depression Subset
ICD	International Classification of Diseases
IQR	Interquartile Range
JBI	Joanna Briggs Institute
KPS	Karnofksy Performance Status
LFT	Liver Function Test
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major Depressive Disorder
MDT	Multi-disciplinary Team
MINI	Mini International Neuropsychiatric Interview
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMDA	N-methyl-D-aspartate
NPRS	Numeric Pain Rating Scale
PaCCSC	Palliative Care Clinical Studies Collaborative
PCOC	Palliative Care Outcome Collaboration
PHQ	Patient Health Questionnaire
PPS	Palliative Performance Scale
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
Q-LES-Q-SF	Quality-of-life Enjoyment and Satisfaction Questionnaire—Short Form
RANZCP	Royal Australian and New Zealand College of Psychiatrists
RCT	Randomised Controlled Trial
REDCap	Research Electronic Data Capture
SaO2	Arterial Oxygen Saturation
SAS	Symptom Assessment Scale

SD	Standard Deviation
SKIPMDD	Subcutaneous Ketamine Infusion in Palliative Care Patients with Advanced Life-Limiting Illnesses for Major Depressive Disorder
SSRI	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressants
TFT	Thyroid Function Test
TIDieR	Template for Intervention Description and Replication Checklist and Guide
TMC	Trial Management Committee
UK	United Kingdom
UTS	University of Technology Sydney
WHO	World Health Organization
WHO PS	World Health Organization Performance Status

Glossary of Terms

Consultation-liaison psychiatry

Consultation-liaison psychiatry, also known as psychosomatic medicine, is a subspecialty of psychiatry that focuses on the care of patients with comorbid psychiatric and general medical conditions.[1] It is a psychiatric subspecialty focusing on the practice of psychiatry in collaboration with a range of other health professionals, usually in a hospital setting.[2]

Clinically significant depressive symptoms

Depressive symptoms that reach a clinically threshold of severity defined by various depressive conditions in: 1) diagnostic criteria, such as International Classification of Diseases (ICD), or Diagnostic Statistical Manual of Mental Disorders (DSM);[3-6] and 2) validated depression-specific screening tool.[4-6]

Depression

A term used to describe: a state of low mood (e.g., sadness, hopelessness, discouragement), which might be normal or pathological;[7] various syndromes consisting of a constellation of symptoms and signs that feature depressed mood (e.g., major depressive episode); or a myriad of clinical disorders (implying certain aetiologies) as determined by a set of diagnostic criteria (e.g., major depressive disorder, adjustment disorder, and depressive disorder due to another medical condition).[7-9] In this thesis, unless otherwise stated, the word "depression" is used synonymously with "clinically significant depressive symptoms".

Disability-adjusted life years (DALY)

The amount of years of healthy life lost to disease and injury.[10]

Extremely short prognosis

Prognosis of life expectancy in the range of days to weeks, often associated with increasing dependence on others for care, worsening symptom burden,

and associated declining functional scores indicative of median survival of one month or less or an absolute survival of two months or less.[11-13]

Palliative care

Palliative care is the active holistic care of individuals with serious health-related suffering due to severe illness, especially those near the end of life. It aims to improve the quality of life of patients, their families and their caregivers.[14]

Palliative care population

Individuals with advanced cancer or non-malignant life-limiting illnesses such as advanced cardiorespiratory, hepatorenal and neurological illnesses not receiving treatment with curative intent.[15-19]

Palliative medicine

Palliative Medicine is the specialist care of people with terminal illnesses and chronic health conditions in community, hospital and hospice settings.[20]

Prognosis

The likely outcome or course of a disease; the chance of recovery or recurrence.[21]

Psychiatry

The branch of medicine focused on the diagnosis, treatment and prevention of mental, emotional and behavioural disorders.[22]

Syndrome

A set of symptoms or conditions that occur together and suggest the presence of a certain disease or an increased chance of developing the disease.[23]

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CHAPTER 1 – INTRODUCTION: BACKGROUND, AIMS, AND METHODOLOGY

1. BACKGROUND

1.1 Depression

Depression is an illness associated with significant morbidity and devastating impacts in society.[1] Not only can it prevent individuals from pursuing their interests and enjoying life, but it is often associated with overwhelming negative emotions (e.g., sense of worthlessness, guilt and desire for hastened death), adversely affecting their ability to function and interact meaningfully with others.[2-4] It can also place a considerable mental health burden on affected individuals' carers, contributing to distress, anxiety and depression.[5, 6] In terms of disability-adjusted life years (DALY), the impact of depression on the general population was on par with Coronavirus Disease 2019 (COVID-19) and lung cancer in Australia in 2022, higher than that of breast and bowel cancers.[7] It is the condition with the highest burden of disease in middle- and high-income countries, and may become the world's leading contributor to burden of disease in 2030, superseding ischaemic heart disease, stroke and motor vehicle accidents.[8]

1.2 Depression and Palliative Care

Palliative care is a specialty that focuses on optimising the function and quality of life of people with life-limiting illnesses, aiming to reduce suffering.[9] For these individuals, there is often a continuum of clinically appropriate versus pathological mood changes.[10] Clinically significant psychiatric co-morbidities such as depression and anxiety are significantly associated with poor quality of life, high physical symptom burden, and low physical and psychosocial functioning in these individuals (level 1 evidence), so the issue of depression warrants attention in the palliative care setting.[10, 11] Depression has devastating impacts for individuals facing advanced life-limiting illnesses, and is common, affecting one in four individuals in this setting.[12] However, research designed to determine the prevalence of depression in palliative care are often challenged by the heterogeneous constructs of "depression" and the "palliative care

population" (i.e. predominantly oncology focused with variable prognoses), resulting in a wide range of results, conservatively ranging from 2% to 30%.[12-21]

1.2.1 The Variability of Depression Definition

The term "depression" can be defined variably in different contexts. The general public often use it to describe a state of mood (e.g., sadness, hopelessness, discouragement), which might be normal or pathological, causing a degree of functional impairment.[22] In comparison, clinicians and researchers often use this term to describe various syndromes consisting of a constellation of symptoms and signs that feature depressed mood (e.g., major depressive episode), or a myriad of clinical disorders (implying certain aetiologies) as determined by a set of diagnostic criteria (e.g., major depressive disorder, adjustment disorder, and depressive disorder due to another medical condition).[22-24]

The gold standard criteria for diagnosing various depressive syndromes and disorders are considered to be the International Classification of Diseases (ICD) and Diagnostic and Statistical Manual of Mental Disorders (DSM), devised by the World Health Organization (WHO) and American Psychiatric Association (APA) respectively.[23, 24] These criteria have evolved in the last decades. After World War II, there was growing recognition of the need for a system to collect statistical information about mental health disorders and perform more systematic assessment of mental health disorders for the purposes of clinical care.[25] Agreement between the ICD and DSM systems was lacking until 1994, when DSM-IV was created, which maps directly to ICD-10.[26, 27] In the Australian and American settings, the DSM system is preferred for clinical purposes, because it offers a more explicit set of criteria for diagnosing depressive disorders, while ICD is predominantly used for coding.[25]

In the palliative care population, depressive symptoms can relate to a myriad of depressive syndromes and disorders. For example, in DSM-V, the diagnosis of the syndrome of a major depressive episode is based on symptoms of depressed mood and/or loss of interest (anhedonia), and the presence of at least another three out of the following seven symptoms for a two-week period: weight or appetite changes; sleep disturbances; psychomotor agitation or retardation; fatigue; feeling of worthlessness or guilt; cognitive changes; and

suicidal risks.[4] Using the clinical features associated with major depressive episode(s), diagnoses of various clinical disorders such as “major depressive disorder”, “bipolar disorder”, “schizoaffective disorder” are then made. Other relevant depressive disorders to consider in the palliative care setting may include depressive disorder due to another medical condition, substance or medication-induced depressive disorder, and persistent depressive disorder.[4] In this thesis, unless otherwise stated, the word “depression” is used synonymously with “clinically significant depressive symptoms”, a term in the literature that embraces various depressive conditions defined by either: 1) diagnostic criteria defining various depressive syndromes and disorders (e.g., ICD or DSM);[28] or 2) validated depression-specific screening tool.[29-31]

1.2.2 The Heterogeneity of the “Palliative Care” Population

In the past, the construct of the “palliative care population”, or the label “terminally ill”, often focused predominantly on people with advanced cancer.[12, 32-36] However, growing awareness of palliative care needs of individuals with advanced non-malignant diseases drove the expansion of clinical palliative medicine to accommodate them (often under the label of “supportive care”).[37-39] In this thesis, the palliative care population includes not only individuals with advanced cancer, but people with non-malignant life-limiting illnesses - such as advanced cardiorespiratory, hepatorenal and neurological illnesses – who are not receiving treatment with curative intent.[6, 16, 40-42]

The “palliative care” population also includes people with advanced life-limiting illnesses at different stages of their disease trajectory, encompassing people with a prognosis in the months to years range as well as those whose death is imminently.[39, 43-45] The sub-group of individuals whose prognoses are extremely short in the range of days to weeks is characterised by high dependence on others for care, frailty, and often worsening symptom burden (e.g., pain, dyspnoea, difficulty with oral intake, cognitive decline and fatigue).[46-48] Functional scores indicative of one month or less of median survival include: Karnofsky Performance Scale (KPS) ≤ 40, Eastern Cooperative Oncology Group (ECOG) 4, and Palliative Performance Scale ≤ 50.[47, 49, 50] Additionally, this period often signals the loss of benefit from treatment of the underlying

diseases, and increased complications (e.g., refractory cachexia).[51] These factors can contribute to the development and escalation of depression in this sub-group (e.g., hypercalcaemia causing pain and depressive symptoms).[52] Therefore, the assessment and management approaches of individuals with extremely short prognoses can differ significantly from those applied earlier in the disease trajectory. This is discussed in more depth in the sections below.

1.3 Prognostic Accuracy

The process of prognostication can be complex. Studies of the accuracy of clinicians prognosticating the survival of people with advanced life-limiting illnesses have yielded mixed results.[53-57] Determinants that may influence the accuracy of prediction in the literature include the clinicians' approaches to prognostication (e.g., probabilistic versus temporal estimation) and experiences, the nature of the life-limiting illnesses (e.g., cancer versus non-cancer), and individuals' co-morbidities and psychosocial factors.[58-60] Despite the availability of multiple prognostic tools, there is evidence that clinical prediction by clinicians remains superior to the use of prognostic tools alone.[57, 61] Nonetheless, the use of prognostic tools to augment clinician prediction of survival may improve accuracy.[54] In fact, clinician prediction may involve a holistic assessment of the individual with an advanced life-limiting illness by the treating clinician, considering the functional status, co-existing symptom burden (e.g., anorexia-cachexia syndrome and cognitive changes), and associated laboratory results (e.g., lymphopenia, hypoalbuminaemia) of the affected individuals.[54, 58] Among these prognostic factors, low functional status is probably the most extensively studied and consistently predictive factor that indicates poor survival.[47, 58]

Despite mixed results about clinicians' prognostic accuracy, the accuracy of clinical prediction of survival when using probabilistic estimation (i.e., estimating in the range of days, weeks and months as in this thesis) remains reasonable with relatively high positive predictive value, especially when the prognosis is extremely short.[62] Hence, a key assumption of the current research was that clinicians can identify and differentiate people with extremely short prognoses from people earlier in the disease trajectory.

Due to various feasibility and ethical concerns (discussed in later chapters), many palliative care studies are conducted in individuals who are relatively well, excluding people with extremely short prognoses.[63-65] These study findings and their implications for care approaches may not be generalisable to individuals at the very end of life. When studying the palliative care literature for symptom management, critical appraisal of the settings and the applicability of such studies in the extremely short prognosis setting is required.

The next section presents a discussion of methods of identifying depression in palliative care.

1.4 Detection, Assessment and Diagnosis of Depression in Palliative Care

While depression seems prevalent in the general palliative care population, its detection, assessment and diagnosis can be difficult. One key challenge lies in how to differentiate the clinical features of depression from those caused by the primary life-limiting illnesses, or other key differential diagnoses. Several approaches (inclusive, exclusive, substitutive and aetiologic) to this challenge are discussed in the literature.[66] Note that while these approaches have been studied in palliative care populations, they have not been exclusively studied in people with extremely short prognoses.

1.4.1 Detection

Many screening methods for depression exist in the general psychiatry literature, but there has been controversy about the appropriateness of including somatic symptoms of depression when applying them to people with advanced life-limiting illnesses.[13, 15, 66-69] Among the myriad of screening tools, only a few have been validated in the general palliative setting, used mainly in the research context (e.g., one or 2 two item questionnaires asking “Are you depressed?” and “Can you still find pleasure in…?”, used either alone or together, the Hospital Anxiety and Depression Scale [HADS], the Edinburgh Postnatal Depression Score, and the Visual Analogue Scale).[70-75] Some screening tools are part of generic symptom screening tools (e.g., Palliative Outcome Scale and Edmonton Symptom Assessment Scale).[76] Others are depression-specific, such as the depression subset of HADS (HADS-D) or the

one- or two-item questionnaire.[70, 73, 77-79] Though there is a lack of head-to-head comparison between these tools, the two-item questionnaire seems to have the highest level of evidence, and is more commonly utilised by clinicians in the general palliative care setting.[79, 80] The screening approaches employed and uptake of these screening tools in the setting of extremely short prognosis by clinicians are currently unknown.

1.4.2 Assessment and Diagnosis

There are multiple classifications systems for the diagnosis of depression, such as DSM, ICD, Endicott, and Research Diagnostic Criteria.[4, 15, 23, 24, 81] In general, the most common method of diagnosing depression in the general palliative care population involves application of the DSM criteria in clinical interviews.[4, 23, 67] More often, in the clinical setting, this is done in a non-structured diagnostic interview exploring the various aspects, impacts and meaning of depression to the affected individuals. This is in contrast to the methods used in research, such as the Structured Clinical Interview for DSM-III-R, which does not have the flexibility required for clinicians to build rapport and may pose extra burden on those affected with depression and life-limiting illnesses.[82] The substitutive approach using Endicott Criteria, in which the symptoms of the advanced life-limiting illnesses (e.g. fatigue, sleep changes, cognitive changes and weight loss) are replaced by other melancholic depressive symptoms (e.g., depressed appearance, social withdrawal, brooding/pessimism, lack of reactivity) based on the DSM criteria seems, anecdotally, to be less widely known and less frequently used in practice.[81]

During depression assessment, the potential causes of depressive episodes are usually explored with the intention of trialling of treatment, if considered appropriate to the individual's goals of care. Some common contributors to depression in the general palliative care setting are: uncontrolled symptom burden (e.g. pain),[83, 84] electrolyte or endocrinological disturbances (e.g. hypercalcaemia and hypothyroidism),[85, 86] neurological diseases (brain metastases or stroke),[87-89] treatment such as glucocorticoid, radiotherapy to the brain and certain systemic anti-cancer therapies (e.g. tamoxifen).[88, 90] The consideration of these potential causes of depression allows clinicians to better

tailor the depression treatment for the affected individuals, maximising benefits and minimising harms.

After depression is diagnosed, depression severity is often assessed in the clinical interview, determining the degree of functional impairment and the risk of harm, in some cases with the input of experienced psychiatric professionals.[10, 67] Sometimes, a validated tool such as the HADS, Beck Depression Inventory, or Hamilton Depression Rating Scale is used to assess depression severity.[10, 67]

While various strategies of detecting, diagnosing and assessing depression in the medically ill setting exist in the literature, there is currently a lack of knowledge about how depression is screened and assessed in people with extremely short prognoses, and whether there are differences in approaches.

1.5 Management

1.5.1 General Approach

Until recently, the management of depression in the palliative care population was largely extrapolated from the non-palliative populations.[91] If deemed appropriate (in line with the individual's goals of care), potentially reversible causes and contributors of depression found during the assessment are treated.[10] Further supportive therapies are given through the foundational use of non-pharmacological interventions, with the addition of pharmacological management if indicated.[13, 36] Depending on the needs of the individuals and the local service resources, it may be beneficial to manage depression in a multi-disciplinary team stting.[92, 93] The team members may include general practitioners, palliative physicians, nurses, pastoral care and social workers, and the mental health team (psychiatrists, mental health nurses and psychologists) as deemed appropriate.[92, 93] However, access to some of these team members, especially the mental health team, is often poor.[67, 69]

1.5.2 Non-pharmacological Interventions

Underpinning numerous non-pharmacological interventions for depression is the use of good communication skills in a therapeutic manner, involving

attentive listening, expression of empathy, the provision of supportive psychotherapy, and education of patients and family.[13, 94] During these sessions, patients may reflect on what is important in their lives (meaning, purposes, and important relationships). Their past experiences of losses, fears, concerns and hopes for the future may also be explored. The sessions often aim to foster a sense of dignity and meaningful connections.[13, 36]

There are many therapeutic non-pharmacological approaches, with many of the psychotherapy approaches requiring 6-8 weeks to complete in the non-palliative setting, but less time in the general palliative care context.[10] Approaches such as supportive expressive psychotherapy,[95-97] cognitive behavioural therapy,[95, 96] and music therapy[98] have a higher level of evidence (level 1 – meta-analysis) about their effectiveness than others in the general palliative care setting, with studies performed mostly in the cancer population without extremely short prognoses. The decision about which intervention is the most appropriate is generally made on a case-by-case basis, tailored to the individual's needs and preferences. Some examples are listed below according to the level of evidence:

- Level 1 - meta-analysis:
    - Psychotherapy: supportive expressive psychotherapy, cognitive behavioural therapy, and problem-solving therapy (advanced cancer population) [95-97]
    - Interpersonal therapy (cancer population) [99, 100]
    - Music therapy (general palliative care and cancer population) [98]
- Level 2/3 Randomised Controlled Trial (RCT) evidence:
    - Dignity therapy (one RCT in palliative care population) [101, 102]
    - Existential /Meaning-in-life therapy (multiple RCTs in advanced diseases) [103, 104]
    - Exercise (two RCT in palliative-rehabilitation, and in people with cancer) [105]
    - Art therapy (multiple RCTs in people with cancer)[33]
    - Life narrative intervention (one RCT in advanced cancer) [106]

1.5.3 Pharmacological Interventions

For patients with depression that cannot be optimally treated with non-pharmacological approaches, concurrent pharmacological interventions are considered,[13] though few RCTs of antidepressants have been specifically completed in the setting of life-limiting illnesses.[13, 107, 108] When choosing antidepressants, it is recommended that clinicians consider their potential additional benefits on co-existing symptoms such as neuropathic pain, insomnia and anorexia.[10] Other important considerations include the likely tolerability of the proposed agent, taking into account the frailty and physiology (e.g., renal and liver function) of the individual, and any potential drug interactions.[109] Selective serotonin reuptake inhibitors (SSRI) are often considered to be first line medications, given their level 1 evidence in effectiveness in the advanced cancer and general palliative care populations. They are generally better tolerated than tricyclic antidepressants (TCA) despite TCA showing higher efficacy in a systematic review involving the general palliative care population.[110-113] Serotonin and noradrenaline reuptake inhibitors (e.g., duloxetine and venlafaxine) are used when there is co-existing neuropathic pain, although there is no RCT data showing their effectiveness in treating depression in the palliative care or advanced cancer population.[114] Monoamine oxidase inhibitors are rarely used due to their potential adverse drug interactions, especially given the proportion of people with a life-limiting illness who need to take an opioid.[109, 115, 116] Tetracyclics like mirtazapine are commonly used to treat depression as well as insomnia and anorexia, which are prevalent in people with life-limiting illnesses.[117-120] Though mianserin has been shown to be more efficacious than placebo, the evidence is scant, with only one RCT demonstrating its effect in stage IV cancer in a systematic review.[113]

Additionally, despite typical antidepressants such as SSRIs and TCAs being shown to be more effective than placebo in the general palliative care population, these antidepressants may have only therapeutic benefit for those with prognoses of more than one month due to the slow onset of action (2-4 weeks).[112] Even assuming the “right” antidepressant is selected, depression remission rates can be as low as one third.[121]

Psychostimulants (e.g. methylphenidate, dextroamphetamine, modafinil) have been suggested for use for their rapid onset of action for patients with prognoses of less than several months.[91, 115] Such medications may also improve fatigue, which correlates with depressive symptoms, though clinical trial data supporting their use is scarce.[115, 122-127] Apart from their often restricted access (e.g. requiring approval under the Special Access Scheme in Australia), their administration, like most typical antidepressants, is constrained to the oral route, and many patients cannot swallow at the end-of-life stage.[48] Consequently, the feasibility of their use in people with extremely short prognoses may be limited.

1.5.4 Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is the most efficacious treatment for major depression, particularly when psychosis, melancholia or medication resistance are evident.[128, 129] However, due to the intrusive and restrictive nature of this intervention (needing to be administered in hospital under general anaesthetic), and the stigma related to the treatment, ECT is rarely administered in the palliative care setting.[115]

1.5.5 Experimental Agents – Ketamine

Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, which has been used predominantly for its anaesthetic and analgesic effects.[130-134] In recent years, there is growing evidence (outlined in Chapter 5 Section 2.3) that ketamine and esketamine are rapid and effective novel agents in the treatment of depression in the psychiatric population, even for those with treatment-resistant major depression who have not responded to the typical antidepressants or ECT.[135-146] These medications, however, have not been tested for this indication in the palliative care population.

1.6 Suboptimal Depression Care in Palliative Care

Despite depression in individuals with palliative care needs being an important issue, it is often under-detected, and even when diagnosed, under-treated.[67, 69, 147-150] In one study, the concordance between patients' reports and oncologists' recognition of moderate to severe depressive symptoms was only 13%.[147]

Surveys of Australasian and United Kingdom (UK) palliative care physicians showed low rates of screening and routine assessment of depressive symptoms in the general palliative care setting, while the majority of depressed patients in palliative care units did not received potentially effective treatments for depression.[67, 68, 149]

Some of the barriers to the optimal depression care in the palliative care setting postulated are:

1. Barriers to detection/assessment:
    - Clinician's factors
        - Fear of distressing patients, especially with the stigma associated with psychiatric diagnoses (e.g., major depression)[13, 115]
        - Lack of awareness and training in the use of assessment tools[67-69, 76, 151]
        - Not recognising depression if the patient is not "crying" or reporting "depressed mood" when depression is severe[147]
        - Not knowing that hopelessness, helplessness, worthlessness, guilt, anhedonia and active suicidal ideation are better indicators for depression than neurovegetative symptoms[36, 152-154]
        - Belief that depression is normal and expected when facing a life-limiting illness [115, 155]
        - Time constraints[67, 68, 155]
    - Low acceptability of the assessment tools
        - Some tools are too long and burdensome for clinical use[71-74, 115]
        - Ultra-short tools (e.g., single item) might not be reliable[71, 78, 156]
    - Perceived lack of benefit of screening in changing the ultimate outcome despite recommendations[76, 151, 157]
2. Barriers to treatments:
    - Clinicians' perspective that treatments might not work in time – a sense of hopelessness and therapeutic nihilism[36]
    - Clinicians' apprehension about possible drug interactions between psychotropics and other symptom medications[115]

- Lack of psychiatric and psychology inputs into the multidisciplinary palliative care team[67, 69]

Caring for individuals with depression in the palliative care setting can also be challenging due to ethical considerations. Considering individuals' autonomy, clinicians might wrestle with the extent to which the desire for hastened death of individuals is respected and how to respond to it.[158, 159] Deciding that individuals with depression should be treated against their wishes, and where (e.g., palliative care unit or mental health unit) they should receive these treatments when they are at risk to themselves or others, can be difficult.[159] Clinicians might also struggle with the ethics of involving individuals in experimental trials for depression at the end of life.[65] Their concerns over individuals' lack of capacity to make informed decisions and the perceived risk of harm may also contribute to their "gate-keeping" of individuals with respect to research participation.[65] At the health service and policy level, the extent to which healthcare resources should be directed towards caring for depression in this palliative care setting when there are many other competing interests (e.g. poorly controlled pain) is uncertain.[160]

1.7 Depression Care in People with Extremely Short Prognoses

While clinical approaches to depression have been studied in palliative care, it is uncertain whether these approaches are applicable to people with extremely short prognoses and whose care needs may be different. Moreover, the prevalence of depression in people with extremely short prognoses is unknown. Escalating fatigue and breathlessness can hinder engagement with various non-pharmacological interventions, limiting their full therapeutic benefits.[47, 48] Meanwhile, the prevalent co-existing organ dysfunctions and inability to swallow potentially restrict individuals' tolerability of many pharmacological interventions, reducing their effectiveness when time pressure is high.[48, 112] Overall, the current literature provides little certainty about which depression interventions, when translated to people with extremely short prognoses, are tolerable, effective and appropriate. There is a need to explore low-burden, rapidly effective interventions that can be well-tolerated in this population.

Similarly, the generalisability of the postulated barriers to optimal depression care in the general palliative care setting when applied to people with extremely short prognoses is questionable. Studies of clinicians' approaches to and perspectives on depression care in the palliative care setting have been conducted among palliative physicians, but not psychiatrists.[67, 69] Thus, there is a need to explore both palliative physicians' and psychiatrists' approaches and perspectives to depression care specifically in the extremely short prognosis setting to optimise patient outcomes in this field.

Left untreated, not only may depressed people with extremely short prognoses experience exacerbation of their physical symptoms, but the associated negative symptoms of anhedonia, guilt, worthlessness, hopelessness and suicidal ideation at the end of life might limit their ability to have meaningful interactions, reducing their quality of life and the mental well-being of their family members.[2, 4, 11, 23, 43, 153, 154, 161, 162] A program to explore the complexities of depression in this setting is needed urgently.

2. RESEARCH AIMS AND OBJECTIVES

The overarching aim of the doctoral program described in this thesis was to explore depression in people with advanced life-limiting illnesses and extremely short prognoses with life expectancy of days-to-weeks of life. The research was designed to establish the prevalence of depression in this population and identify effective interventions, clinicians' approaches to and perspectives on delivering care, and the feasibility of studying subcutaneous ketamine as a potentially tolerable and rapid-onset antidepressant in this context.

Specifically, the objectives were to determine:

1. The prevalence of depression (and indirectly, the validated methods being used to screen and assess depression), and the effective interventions available for people with advanced life-limiting illnesses and extremely short prognoses described in the international literature
2. Palliative care physicians' and psychiatrists' current clinical practices and perspectives related to screening, assessment, diagnosis and

management of depression in the palliative care population with extremely short prognoses in the Australasian context

3. The feasibility, safety, tolerability, acceptability and activity of individually tailored subcutaneous ketamine as a treatment for major depressive disorder in people with advanced life-limiting illnesses and extremely short prognoses

3. RESEARCH METHODOLOGY AND DESIGN

3.1 Tansella and Thornicroft's Matrix Model

Tansella and Thornicroft's nine-cell matrix model (1998) for mental health systems of care can be used to guide mental health service reform.[163] It has been used to comprehensively assess the mental health system, and is intended to assist clinicians, planners and researchers to deal with clinical phenomena, organisational issues, and research questions that share a degree of complexity, in settings where interventions and subsequent analyses made at only one level are often inadequate.[163, 164]

This framework describes the considerations of any critical issues relating to the improvement of mental health care with respect to geographical and temporal dimensions.[163]

The geographical dimension considers the levels at which the critical issue of mental health care needs to be considered, namely country, local health service, and patient. At the country level, policies, guidelines and laws are based on the scientific literature. Professionals or clinicians deliver healthcare services that comply with the guidelines and policies in the local health service. Finally, the healthcare services affect the health and well-being of individual patients.

The temporal dimension contains three working phases that leads to the final product of mental healthcare delivery:

(A) Input: the resources required to be injected into the health system (e.g., financial and staffing resources, training and skills of clinicians, and integration of general and specialist services)

(B) Process: the activities involved in the provision of the mental healthcare (e.g., interventions for depression)

(C) Outcome: changes in functioning in morbidity and mortality levels

In the research described in this thesis, Tansella and Thornicroft's matrix was used to underpin the understanding of the complex multi-level interactions for issues surrounding suboptimal depression care delivery in people with advanced life-limiting illnesses and extremely short prognoses. In particular, these issues may involve interactions between: the broader international and literature contexts in which depression care is delivered (international literature/country level – row 1 of matrix); the local Australasian health services and clinicians who deliver the care (local level – row 2 of matrix); and people with depression and extremely short prognosis (patient level – row 3 of matrix).[163] These concepts are detailed in Table 1.1 and discussed in more depth below.

TABLE 1. 1. ADAPTED VERSION OF TANSELLA AND THORNICROFT'S MATRIX

	Temporal Phase		
Geographical Dimension	(A) Input	(B) Process	(C) Outcome
(1) International Literature (Systematic Reviews)	Prevalence of and effective interventions for depression is unknown	Lack of consistency and guidance re optimal methods of screening, assessment and management for depression	Depression-related outcome not known
(2) Local – Australasian context (Clinician mixed-methods study)	Possibly inadequate resources, access and linkages between palliative care and psychiatry, and poor clinician training & support in this field	Little known about local clinicians' approaches, perspectives and challenges re screening, assessing and managing depression	Potential improvement strategies for better depression care delivery in the extremely short prognosis setting unknown
(3) Patient (Phase II pilot feasibility study)	Little known about their needs / characteristics	Feasibility / appropriateness of various screening, assessment, and treatment approaches uncertain	Responses (effects and tolerability) of depression interventions on people with extremely short prognoses unknown

At the international literature level, ("country" – row 1), little is known about the true prevalence of depression in people with life-limiting illnesses and extremely short prognoses, and how it compares to people with better prognoses (1A). This is likely reflective of the lack of consistency in and guidance on the methods of screening and assessing for depression in this setting; no systematic literature has reviewed explored this topic (1B). Although there is a European guideline for the management of depression in palliative care, there is not yet a clear guideline specific to those with extremely short prognoses, possibly due to the lack of synthesised evidence in this field (1B).[10] Consequently, the outcome for people with depression and extremely short prognosis at the population level is unclear (1C).

At the local service delivery level in Australasia (row 2 of the matrix), the resources and linkage between psychiatry and palliative care, as well as clinician training and support, are perceived to be inadequate (2A).[165, 166] Little is understood about how clinicians in Australasia, especially palliative care

physicians and psychiatrists, approach and view depression in people with extremely short prognoses (2B).[67] Their challenges have not yet been formally studied, and thus ways to optimise service delivery in this area are uncertain (2B, 2C). While all members of a multidisciplinary palliative care or psychiatry team would deliver care for someone with depression, due to the time and resource limitations of a doctoral program, the perspectives of the medical professionals who prescribe interventions were the priority and focus of this PhD study.

At the patient level (row 3 of the matrix), few studies illustrate the needs and characteristics of people with depression and extremely short prognoses (e.g. their ability to engage and comply with potentially useful interventions, or the prevalence of treatment resistant depression).[149] The feasibility of screening and assessment methods for individuals with extremely short prognoses is questionable due to the symptom burden from terminal illnesses and their confounding effects with the somatic symptoms of depression.[13, 76] Not only does individuals' frailty make assessments more difficult, it may reduce their ability to comply and engage with courses of potentially effective interventions (such as psychotherapy or typical antidepressants) to receive therapeutic benefits (3C). Accordingly, the efficacy and tolerability of depression interventions for people with extremely short prognoses are currently unknown (3C).

3.2 Research Design & Chapter Overviews

Underpinned by the conceptual framework of the Tansella and Thornicroft matrix, the doctoral project utilised quantitative and qualitative study designs to reach its objectives.[163] It consisted of the following studies.

Systematic Reviews – of the prevalence of and effective interventions for clinically significant depressive symptoms in people with advanced life-limiting illnesses and extremely short prognoses in the international literature (Chapter 2 and 3). The work presented in these chapters found clinically significant depressive symptoms to be highly prevalent among these individuals, and that randomised controlled trial evidence to support interventions in this context is lacking.

Mixed-Methods Study – a predominantly quantitative survey and a subsequent qualitative focus group study (sequential explanatory design) of current palliative physicians' and psychiatrists' approaches to and perspectives on caring for depression in people with advanced life-limiting illnesses and extremely short prognoses in the Australasian context (Chapter 4). This chapter demonstrates the complexity and challenges palliative physicians and psychiatrists perceive in caring for these people, highlighting the need for improved training, access to interventions, linkages between services, research support, and cultural attitudes. It also presents the integration of the care processes of existing palliative care and psychiatry services as a potential improvement strategy.

Phase II Feasibility Study – **SKIPMDD: S**ubcutaneous **K**etamine **I**nfusion in **P**alliative Care Patients with Advanced Life-Limiting Illnesses for **M**ajor **D**epressive **D**isorder (Chapter 5). This chapter presents the findings that a future definitive trial of the use of subcutaneous infusion of ketamine for major depressive disorder in the palliative care setting may be feasible, and that individual dose-titration starting from ultra-low dose of 0.1mg/kg over two hours can be well-tolerated while producing transient antidepressant effects over hours to days.

The knowledge gained from these studies was integrated using the modified Tansella and Thornicroft matrix to inform the methods of assessment and diagnosis of depression in people with advanced life-limiting illnesses and extremely short prognoses, its prevalence, any effective therapies, the perspectives of palliative physicians and psychiatrists on delivering care, and the feasibility of studying subcutaneous ketamine as a potentially tolerable and effective antidepressant (Chapter 6).

4. SIGNIFICANCE

This doctoral program provides critical information that will allow clinicians, service leaders, funders, policy makers and researchers to optimise depression care delivery in the setting of extremely short prognoses. Ultimately, the knowledge acquired from this program may underpin strategies to improve depression-related outcomes for those affected and their important persons,

relieving suffering and restoring quality to the precious life remaining to these people.

5. THE IMPACT OF COVID-19

The COVID-19 pandemic disrupted this doctoral program significantly. The candidate and research and clinical colleagues were required to focus on COVID-19-related activities (clinical work, home schooling, and COVID-19-related research and guideline development), causing several delays and changes in the doctoral program.

For the systematic reviews (Chapter 2 and 3), the investigator team members were requested to prioritise clinical activities related to COVID-19, delaying high-level and detailed full text screening for many months. After the completion of systematic reviews and writing up results for publication, editors informed the authorship team that manuscript reviews would be delayed due to the impacts of the pandemic. Subsequently, one initial submission could not meet the journal's data currency requirement, requiring a second search of electronic databases, delaying review and acceptance for at least one year. The dissemination of the research findings was hindered by an oral conference presentation being cancelled due to the COVID-19 pandemic.

For the mixed-methods study (Chapter 4), COVID-19 caused a delay of several months in professional bodies distributing the online survey link, and the participation rate for survey was sub-optimal, especially from the psychiatric cohort. Subsequent focus group participants postulated that this was due to clinicians focusing on COVID-19-related activities and regarding research as a non-essential activity. Due to pandemic-related restrictions, the decision was made to change the planned face-to face focus groups to online focus groups. In order to salvage the focus group study, inclusion criteria were broadened to include participants who had yet to complete the preceding survey. The low sample sizes might have limited the degree of variation in the views expressed and data saturation in the mixed-methods study.

Similarly, recruitment for the phase II feasibility study (Chapter 5) was intermittently suspended for months at various sites due to the COVID-19

outbreak. This study was also hampered by the loss of research nurse positions due to the halting of clinical trials and the difficulty of reviewing participants in person in light of changing hospital COVID-19 policies. Ultimately, this contributed to the small sample size achieved over the two-year study period.

It was intended that a Delphi study involving psychiatry and palliative care clinicians would be undertaken using the findings from the studies above to create consensus and recommendations for the screening, assessment, and management of depression in individuals with advanced life-limiting illnesses and extremely short prognoses. Due to unexpected delays related to the COVID-19 pandemic, the Delphi study was removed from the doctoral program to allow focus on the studies that had been completed.

CHAPTER 2 – THE PREVALENCE OF CLINICALLY SIGNIFICANT DEPRESSIVE SYMPTOMS IN PEOPLE WITH EXTREMELY SHORT PROGNOSES

1. PREFACE

Chapter 1 provides an introduction to depression in the extremely short prognoses setting, describes the issues with screening, assessment and management, and gives an overview of the doctoral program and study designs. Chapter 2 presents a systematic review of international literature on the prevalence of clinically significant depressive symptoms among people with extremely short prognoses.

This chapter contains the following article (reproduced in Appendix 1) published in 2021 in *Journal of Pain and Symptom Management*, formatted to conform to the thesis guidelines:

Lee, W., Pulbrook, M., Sheehan, C., Kochovska, S., Chang, S., Hosie, A., Lobb, E., Parker, D., Draper, B., Agar, M. R., & Currow, D. C. (2021). Clinically significant depressive symptoms are prevalent in people with extremely short prognoses - a systematic review. *Journal of Pain and Symptom Management* **61**(1): 143-166.e142.

2. INTRODUCTION

Previous prevalence studies and systematic reviews of the prevalence of depressive symptoms in the palliative care and oncology settings reported a prevalence of depression to be between 2%-30%.[12-18, 167, 168] However, these studies did not explicitly examine prevalence in people with extremely short prognoses.[12, 14] Additionally, studies included in these reviews focused on specialist palliative care and oncology cohorts.[12, 14] Patients with advanced non-malignant life-limiting illnesses and extremely short prognoses outside these services would have been excluded. Complicated by the heterogeneity of definitions of depression and the numerous depression assessment methods mentioned across the literature mentioned in Chapter 1, the identification and diagnosis of depressive syndromes in this context were even more difficult.

Subsequently, the prevalence of clinically significant depressive symptoms in the extremely short prognosis setting is currently unknown.

For the purpose of this review, consistent with the literature, the term “clinically significant depressive symptoms” will be used. This term embraces various depressive conditions defined by either: 1) diagnostic criteria, such as ICD, or DSM;[28-31] and 2) validated depression-specific screening tool. The inclusion of prevalence defined by depression-specific screening tools would ensure clinically significant depressive symptoms that fulfil specific cut-offs of screening tools but not the conventional diagnostic criteria due to the extremely short prognoses (i.e. sub-syndromal depression) are accounted for.

Knowledge of the prevalence of clinically significant depressive symptoms in people with extremely short prognoses would quantify its global burden and inform screening, assessment and impetus for developing targeted therapies.

3. AIM

To determine the prevalence of clinically significant depressive symptoms in people with extremely short prognoses (median survival of ≤ 4 weeks with absolute cut-off of < 2 months) suffering from advanced life-limiting illnesses, as indicated by survival or functional status data (Karnofsky Performance Scale [KPS] ≤40 or equivalent).[49, 50, 58, 169]

4. METHODS

4.1 Design & Protocol Registration

Systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[170] The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42019125119).

4.2 Search Strategy

A systematic search of the electronic databases of MEDLINE (OVID), PsycINFO, Embase, CINAHL, and CareSearch (CareSearch filter utilised via

PubMed) for studies published between January 1994 and February 2019 was performed (last search 27 February 2019). The search was limited to the last 25 years, as 1994 was the year when DSM-IV was assimilated to ICD-10 to ensure congruence.[26]

The search strategy included search terms in the domains of [Palliative Care or Advanced Life-Limiting Illnesses] AND [Prevalence] AND [Depression] was used initially in MEDLINE (OVID), with the search terms adapted for other electronic databases accordingly (see 'Search Strategy' in Appendix 2).

Inclusion criteria for studies were: any setting of care or study design; adults (≥ 18 years) with advanced life-limiting illnesses and extremely short prognoses in the range of days to weeks defined by either survival data (absolute survival of <2 months) or functional status indicative of a median survival of 1 month (equivalent of AKPS ≤ 40 or Eastern Cooperative Oncology Group (ECOG) 4);[49, 50, 58, 169] and prevalence of clinically significant depressive symptoms defined by a validated tool (e.g. Hospital Anxiety and Depression Scale [HADS]) or a depressive disorder defined by diagnostic criteria (DSM or ICD or equivalent). In relation to diagnostic criteria, the term "major/minor depression" will be used in this review to encompass: 1) Both "major/minor depressive disorders" and "major/minor depressive episodes" in DSM[4, 23]; and 2) "major/minor depression" in ICD.[24]

Excluded studies were those not peer-reviewed (e.g., studies with no validated method of assessing depressive symptoms; studies using measures not specific to depression (e.g., Edmonton Symptom Assessment Scale); as well as systematic reviews and meta-analyses, case studies, opinion papers, editorials, study protocols or guidelines. A manual selection for adult, human and English studies was performed without the use of filters to minimise the risk of missing articles due to delayed coding issues. The reference lists of relevant systematic reviews and meta-analyses were hand-searched for eligible studies.

4.3 Study Selection

Search results were imported into Endnote X9.2 for duplicate removal, and subsequently exported to Covidence for title and abstract, and full text screenings.[171, 172]

Each study was reviewed by both the primary investigator (WL) and a reviewer from the alternative reviewer group (MP, CS, EL, AH, DP, MA, SK) with reasons for exclusions at full text review documented. A third independent reviewer (BD) was involved in resolving conflict.

4.4 Data Extraction

Data extracted from individual studies included: country; study design; eligibility of sampled population; settings; diagnoses; participant demographics; sampling method; definition and number of participants with extremely short prognoses; depression definition, assessment timing and method; and number and prevalence of clinically significant depressive symptoms in people with extremely short prognoses. When necessary, the authors of the publications were contacted for clarification of the data.

Quality and risk of bias assessments were performed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools for use in JBI Systematic Reviews - Checklist for Prevalence Studies (for individual studies)[173, 174] and the principles of Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (across studies).[175, 176]

The primary investigator (WL) extracted data from all included studies. Alternative reviewers (MP and AH) checked the validity of extracted data and independently performed quality/bias assessment of studies by randomly selecting studies using a random number generator. Given that 100% consensus was reached on discussion after randomly reviewing five of the 13 studies, remaining studies were only reviewed by the primary investigator (WL).

4.5 Data Synthesis

Prevalence rates were calculated from the number of cases with clinically significantly depressive symptoms and extremely short prognoses over total number of cases with extremely short prognoses in each included study. Random effects models were used in accordance with the method of Nyaga et al (2014) to produce pooled prevalence estimates for clinically significant depressive symptoms defined by specific screening tools and diagnostic criteria.[177, 178] The I^2 statistics were used to estimate heterogeneity and risk of bias. Potential sources of heterogeneity were further investigated by use of visual inspection of the data, forest plots and through meta-regression analysis. Analyses were carried out with the function for proportion meta-analysis in STATA Version 16.0.

5. RESULTS

As outlined in the PRISMA diagram (Figure 2.1), 7957 studies were identified through the electronic databases. After removal of duplicates, 5531 studies underwent title and abstract screening, leaving 500 studies for full-text screening. Following this, 13 studies (Table 2.1) were included for data extraction, with 57.1% (278 out of 487) full-text screening studies not having data on the sub-group of interest (people with extremely short prognoses). Hand-searching did not identify any eligible studies.

Study demographics were illustrated in Table 2.2. All 13 included studies had a prospective design, with five studies[179-183] being longitudinal and eight being cross-sectional only.[2, 84, 184-189] Two studies had a combination of malignant and non-malignant diseases (e.g., cardiovascular, respiratory and other diseases).[84, 189] Ten studies only focused on malignant disease.[2, 179, 180, 182-188] Out of these, one study focused on advanced gynaecological cancer[188] and another on lung cancer.[182] Other eight malignant studies involved a combination of various types of cancers.[2, 179, 180, 183-187] Extraction of data of interest from specific malignant or non-malignant conditions in studies involving combination of conditions was not possible. Only one study focused exclusively on a non-malignant disease (late stage amyotrophic lateral sclerosis).[181]

Six studies only involved inpatients[2, 179, 183, 184, 188, 189], of which three were palliative care specific.[2, 183, 188] One studies was home care only (palliative care specific).[84] Four studies were mixed settings,[180, 185-187] one of which was palliative care specific.[185] Two studies did not specify the setting of care.[181, 182]

Mean age reported in eight studies ranged from 58.0 to 70.9 years old. Five studies did not report mean age. The percentage of males ranged from 36.5% – 69.8% in 11 studies, with one study not reporting participant gender,[180] and one study only recruiting females with advanced gynaecological cancers.[188]

For the definition of extremely short prognoses, seven studies reported functional status equivalent of AKPS ≤ 40 (median survival of one month),[182-188] and eight studies reported directly on survival data.[2, 84, 179-181, 183, 185, 189] Two studies reported both survival and functional status data.[183, 185]

Ten studies defined clinically significant depressive symptoms using a specific tool: Patient Health Questionnaire 8 or 9 [PHQ-8 or 9] (n = 5),[180, 181, 186, 187, 189] HADS (n = 4),[179, 182, 185, 188] and Depression Rating Scale [DRS] (n = 1).[84] Four studies used diagnostic criteria (DSMIIIR, IV or V),[2, 183, 184, 189] while one study used both PHQ-9 and DSMV.[189]

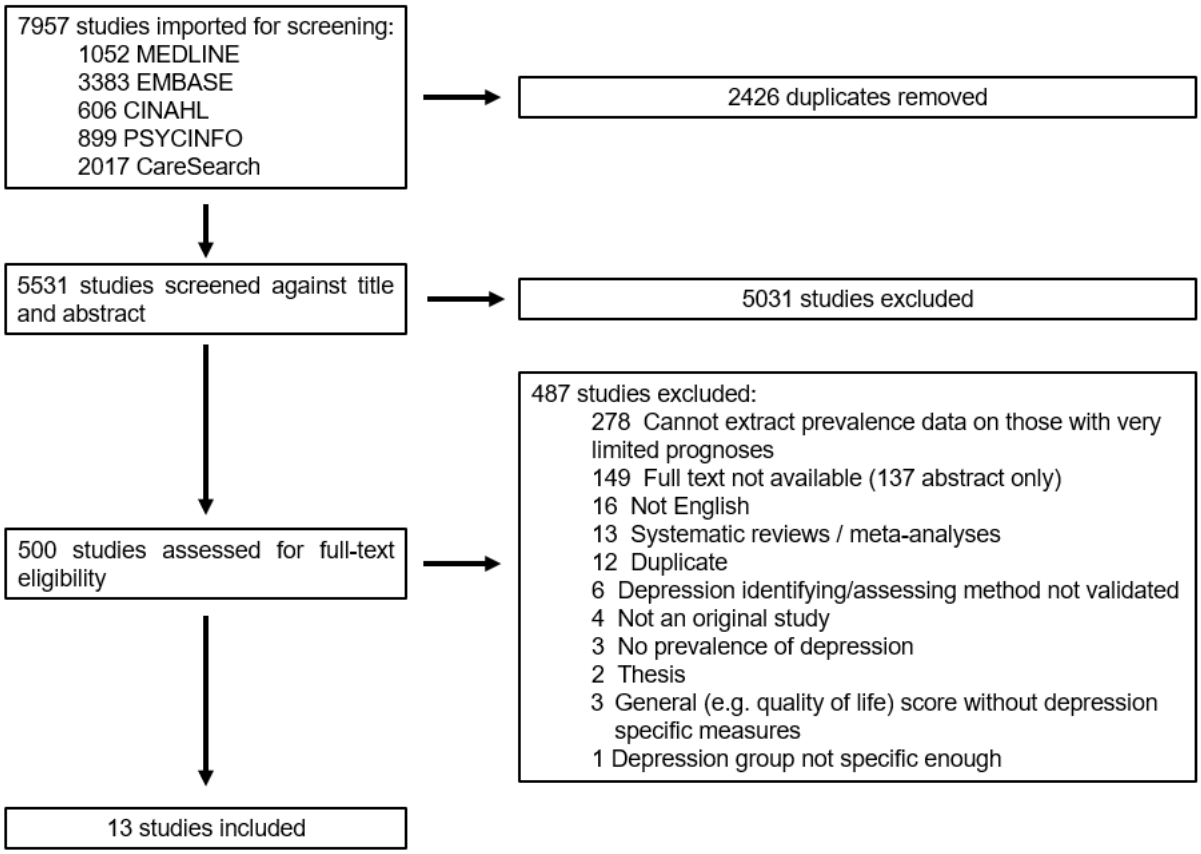


FIGURE 2. 1. PRISMA FLOW DIAGRAM[170]

Caption: PRISMA diagram: 7957 studies were identified through the electronic databases. After removal of duplicates, 5531 studies underwent title and abstract screening, leaving 500 studies for full-text screening. Following this, only 13 studies were included for data extraction. Out of the 478 articles excluded: 57.1% (278 out of 487) of full-text screening studies did not have data on the sub-group of interest (people with extremely short prognoses); 149 articles had no full text (majority were abstracts or posters only); 16 were not English; 13 were systematic reviews/ meta-analyses; 12 were further duplicate identified; 4 were not an original study; 3 Had no prevalence of depression; 2 were thesis; 3 were general score without depression specific measures; and 1 study had depression group not specified well enough.

TABLE 2. 1. CHARACTERISTICS OF INCLUDED STUDIES

Author Year	Location, Country	Study Design	Source Population Eligibility / Recruitment Setting	Diagnoses	Demographics of Source Population (Total number [N), Age, Gender)	Sampling Method	Definition of Extremely short prognoses / Number from Source Population	Depression Definition / Assessment Timing & Method	Number (n) and Prevalence (%) of Clinically Significant Depressive Symptoms in People with Extremely short prognoses
Alamri et al 2017 [189]	Jeddah, Saudi Arabia	Prospective Cross-sectional Prevalence Study	Elderly patients aged 60 years and older admitted to the medical (51%) and surgical wards (49%) of a single university hospital. Exclusion: severe cognitive dysfunction, acute psychosis, bipolar disorder, schizophrenia, language barrier, aphasia, hearing impairment, reduced level of consciousness, or unstable medical illnesses	Cancer (not otherwise specified) and mixed non-malignant diseases (Cardiovascular, gastrointestinal, genitourinary, infectious, metabolic-endocrine, musculoskeletal, neurological, respiratory, and other)	N = 200 Mean age: 70.2 (SD: 8.1) Male = 41.0%	Consecutive	Hospital mortality /Survival (Author responded in email stating all those with hospital mortality had survival <60 days) N = 19	1. Self-administered PHQ-9: • ≥10: "major depression" • ≥ 5-9: "other depressive disorders" 2. Structured clinical interview with DSMV for "major depressive disorder" Within 48 hours of hospital admission by a trained research team member.	PHQ-9 ≥10: n = 6 (31.6%) PHQ-9 ≥ 5-9: n = 2 (10.5%) DSM5 Major Depressive Disorder: n = 1 (5.3%)
Breitbart et al 2000 [2]	New York, United States	Prospective Cross-sectional Prevalence study	Hospitalised, terminally ill cancer patients recruited after admission to a 200-bed palliative care hospital with life expectancy of less than 6 months. Inclusion: English speaking; sufficiently cognitively intact to provide informed	Cancer (not otherwise specified)	N = 92 Mean age: 65.9 (SD: 15.6) Male = 40.0%	Unclear	Survival with average time until death was 28 days N = 89 (interviews could not be completed for 3 subjects)	DSMIV for "major depressive episode" After admission jointly by two investigators via structured clinical interview (interrater reliability coefficients 0.55).	DSMIV major depressive episode: n = 15 (16.9%)

			consent and valid data; and were not considered likely (by their physician) to suffer psychological harm from participation. Exclusion: Mini-Mental State Examination score below 20.						
Chan et al 2012 [188]	Hong Kong, China	Prospective Cross-sectional study	Adult patients (≥18 years) with advanced (Stage III-IV) gynaecological malignancy in the palliative phase admitted to the palliative care unit of Grantham Hospital, Hong Kong. Inclusion: Chinese descent; fluent in the Cantonese dialect; and being capable of giving informed consent to participate in the study. Exclusion: Unable to complete the questionnaires due to either physical or cognitive limitation; and being unable to communicate either verbally or in writing.	Gynaecological cancers (ovary, cervix, uterus)	N = 53 Mean age: 62.1 (SD: 15.5) Male = 0%	Consecutive	Functional status: median PPS = 40 N= 53	HADS (Chinese Cantonese version – Cronbach's α=0.77): • 8 to 10: "doubtful case" • 11 or higher: "definite case" • 15 or higher: "severe depression" Within 3 days of admission interviewed by principal investigator	HADS score: • 11 or higher "definite case": n = 33 (62.2%) • 15 or higher "severe depression": n = 10 (19%)
Chochinov et al 1995 [183]	Winnipeg, Canada	Prospective longitudinal prevalence study	Terminal cancer adult patients from palliative care units of two hospitals in Winnipeg, Canada. Exclusion: Cognitively impaired and unable to give informed consent or were too gravely ill to take part in a detailed interview.	Mix cancer types (lung, gastrointestinal, genitourinary breast, hematological and other)	N = 200 Mean age: 70.9 (SD: 10.6) Male = 48.5%	Unclear	Survival: Median of 43 days Functional status: mean KPS 40 N = 200	DSMIIIR: Major and Minor Depressive Episodes One week or more after admission using semi-structured diagnostic interview administered by a trained psychiatric nurse, clinical psychologist or a psychiatrist. Two-week follow-up interview conducted only for those with	DSMIIIR: • Major depressive episode: n = 16 (8%) • Minor depressive episode: n = 9 (4.5%)

								desire to die at the initial interview. Inter-rater reliability measured by having second rater attend 13.5% of random sample interview (kappa 0.76).	*Cannot extract prevalence data of extremely short prognosis on the two week follow-up time point (as only those with desire for death were re-assessed and reported).
Fisher et al 2014 [84]	Ontario, Canada	Prospective Cross-sectional Prevalence Study	Home care palliative care adult patients in 6 of 14 sites in Ontario involved in pilot implementation of new palliative care need assessment tool (InterRAI Palliative Care) with a mix of malignant and non-malignant diseases. *"Participants were classified as palliative by the home care case manager if they were no longer responsive to curative treatment, considered to be dying, and the goal of care was to alleviate distressing symptoms in the last stage of their illness" Exclusion: Significant cognitive impairment (i.e., Cognitive Performance Score [CPS] < 4); Unable to give informed consent	Cancer (not otherwise specified) and non-malignant diseases (Cardiovascular, Chronic Obstructive Pulmonary Disease, and other)	N = 5144 Average age of 70.0 (range: 19.6 – 107.2; two-thirds of the sample > age 65) Male = 49.1%	Unclear	Survival: Estimated prognosis <6 weeks N = 358	Depression Rating Scale (DRS) (InterRAI Palliative Care) ≥ 3 for "Depressive Symptoms" Assessor rating at time of assessment not otherwise specified	Table 1: "Depressive Symptoms" by Depression Rating Scale (DRS) (InterRAI Palliative Care) ≥3: n = 74 (20.7%)
Hartung et al 2017 [187]	5 regions across Germany	Prospective Cross-sectional Prevalence study	Adults (age 18 through 75), proficient in German, with cancer from a mixture of clinical settings - total of 84 inpatient oncology wards, outpatient clinics, cancer rehabilitation centres in five distinct	Mix cancer types (thyroid, brain, pancreas, hematological, female genital	N = 4020 Mean age: 58 (SD: 11)	Consecutive	Functional status: ECOG4 N = 13	PHQ-9 ≥10 for "depressed" (German version of the self-report measure) Timing of assessment not specified	"Depressed" by PHQ-9 ≥ 10: n = 6 (46.2%)

			regions across Germany (Freiburg, Hamburg, Heidelberg, Leipzig and Wu¨rzburg). Exclusion: Cognitive and verbal impairments that interfered with ability to give informed consent.	organs, bladder, lung, stomach/esophagus, head and neck, soft tissue, breast, testis, kidney/urinary tract, colon/rectum, hepatobiliary, melanoma, prostate, other)	Male = 48.6%				
Hopwood & Stephens 2000 [182]	United Kingdom	Prospective – Longitudinal Prevalence Study using data from 3 RCTs	Adults with lung cancer (non-small-cell and small-cell lung cancers) from three multicentred RCTs by United Kingdom Medical Research Council Lung Cancer Working Party: two chemotherapy trials (LU12 and LU16) and one radiotherapy trial (LU13).	Non-small-cell and small-cell lung cancers	N = 1189 (Male = 69.8%), consisted of the below: LU12 (Chemotherapy trial for small-cell lung cancer): N = 310 Median age: 65 (Range 39-90) Male = 63% LU 16 (Chemotherapy trial for small cell lung cancer)	Random	Functional status: WHO PS 4 N = 11	HADS for “Depression” (“Borderline” or “Case”): • 8-10: “Borderline” • ≥11: “Case” HADS assessed at baseline and at first follow-up	“Depression” (case or borderline score) by HADS ≥8 at baseline: n = 6 (55.0%) *Cannot extract data of extremely short prognosis on the first follow-up time point (High attrition rate with WHO PS 4 prevalence data not reported)

					N = 370 Median age: 67 (Range 35-83) Male = 63% LU13 (Radiotherapy trial for Non-small-cell-lung cancer) N = 509 Median age: 66 (Range: 33-89) Male = 79%				
Que et al 2013 [186]	Manila, Philippines	Prospective Cross-sectional Prevalence Study	Adults oncology inpatients and outpatients presented for cancer treatment at a single non-profit tertiary hospital in Manila, Philippines.	Mixed Cancer Types (breast, head and neck, lung, brain, lymphoma, leukemia)	N = 271 *Age ≥ 53 = 53.5% *Male = 36.5% (*Age & Gender data extrapolated from table 2 of article)	Unclear	Functional status: ECOG 4 N = 7	"Depression" by PHQ-8 (excludes the item on suicidal ideation) ≥10 (Cronbach's α = 0.84) Timing of assessment (survey) not specified	"Depression" by PHQ-8 ≥10: n = 6 (86%)
Rabkin et al 2005 [181]	New York, US	Prospective Longitudinal Prevalence Study	Hospice eligible adult patients with late stage amyotrophic lateral sclerosis (ALS) indicated by FVC <50% ("a value related to the risk of hospice admission and death	Late-stage amyotrophic lateral sclerosis	N = 80 Age ranged from 27 to 85,	Unclear	Survival: Median interval between time of last monthly interview and death = 30 days	Major and Minor Depression by PHQ-9*:	Depression (Both major and minor Depression) by PHQ-9≥6: n = 17 (32.1%)

			or the need for mechanical ventilation within 6 months") from multiple sites (though 94% enrolled from a single ALS Research Centre) (setting not otherwise specified). Exclusion: dementia; inability to speak English; absence of nonpaid caregiver who agreed to participate; use of mechanical ventilation at baseline; inability to communicate at least "yes" and "no,"; lived outside 3-hour drive from medical centre.		20% were under age 50, and one-third were over 70 Male = 56%		N = 53	• Major Depression: ≥5 items with score ≥2 with ≥ 1 item being depressed mood or anhedonia • Minor Depression: ≥3 items with score ≥2 with ≥ 1 item being depressed mood or anhedonia *Authors departed from the standard scoring on three items of PHQ-9 that were sometimes directly caused by ALS: sleep problems, poor appetite, and psychomotor retardation when considered inappropriate, and prorated the remaining items to generate a total score. Scheduled monthly interviews almost always at home until patients met a study endpoint of tracheostomy or death	
Rabkin et al 2009 [180]	New York/San Francisco, United States	Prospective Longitudinal Prevalence Study	Cancer patients with prognosis of 6-12months from oncology services of multiple sites and home care service of a community hospital. Exclusion: Non-English speaking; insufficient cognitive capacity to consent to study; had no a family member or close friend who served as a non-paid caregiver and who agreed to participate; not lived at home within an hour drive from the respective medical centre at study entry	Mixed cancer types (breast, lymphomas, colorectal, lung, pancreas and other)	N = 58 Age and gender of the cohort not reported	Convenience	Survival: Median interval between final assessment and death = 28 days N = 24	"Major depressive disorder" by PHQ-9 ≥10: (≥ five items including depressed mood or loss of interest must be scored 2 or 3) (Cronbach α = 0.79) Assessment by interviews almost always at home scheduled at approximately 1-month intervals until death or the study ended	Major depressive disorder by PHQ-9 ≥10: n = 7 (29.2%)

Stromgren et al 2002 [185]	Copenhagen, Denmark	Prospective Feasibility /Cross-sectional Prevalence study	Danish speaking adult patients with advanced cancer for which no curative or life-prolonging treatment could be offered and referred/admitted to the palliative care services of a Copenhagen hospital (Mixture of inpatient, outpatient and home care palliative care services). Exclusion: No informed consent; staff judged the patient too ill to participate	Mixed cancer types (brain, head and neck, gastrointestinal tract, respiratory, breast, genitourinary, gynaecological, sarcoma, melanoma/skin, hematologic, unknown)	N = 176 Age: mean 62.9 (No SD reported); median 63 (Range: 37-91) Gender: Male = 43.8%	Consecutive	Survival from first contact with department: Median 35 days Functional status: Median KPS 40 N = 134	"Depression (Definite case)" by HADS ≥ 11 Assessed via self-assessment questionnaire at first contact with the palliative care department.	Depression (Definite case) by HADS ≥ 11: n = 63 (47.0%)
Tang et al 2016 [179]	Taiwan	Prospective Longitudinal prevalence study	Adult (≥20 years old) oncology patients with terminal stage cancer and palliative intent treatment (unresponsive to curative cancer treatment and continuing to progress) from medical inpatient units of a medical centre in Taiwan Exclusion: Cognitively incompetent as evaluated by their primary physicians; ability to communicate coherently with data collectors.	Mixed cancer types (lung, liver-pancreas, head and neck, other)	N = 325 Age over 56 years old = 58.5% Male = 57.5%	Convenience	Survival - Time before death of 1-30 days N = 233	"Severe Depressive Symptoms" by HADS scores ≥11 Participants were interviewed while hospitalised or waiting for outpatient visits approximately every 2 weeks until they declined to participate or died.	"Severe Depressive Symptoms" by HADS scores ≥11: n = 192 (82%)
Zhao et al 2014 [184]	Beijing, China	Prospective Cross-sectional Study	Consented adult (≥18 years) cancer patients from the inpatient oncology ward of a hospital in Beijing Exclusion: Too frail or unwell to be interviewed; obvious cognitive impairment based on a brief clinical interview performed immediately before the administration of the Mini International Neuropsychiatric Interview (MINI) 5.0; severe hearing/speech impairment that	Mixed cancer types (lung, digestive tract, breast, liver, ovarian, uterine and other)	N = 460 Mean age: 59.4 (SD: 12.0); Range: 20-99 Male = 49.1%	Consecutive	Functional status: ECOG 4 N = 51	"Depressive Disorders*" by DSMIV ascertained by Chinese version of the Mini International Neuropsychiatric Interview (MINI) 5.0 by eight trained psychiatrists (coefficients of interrater and test–retest reliability were 0.92 and 0.98 respectively). *Depressive disorders included: major depressive disorder (MDD),	"Depressive Disorders*" by DSMIV (MINI): n = 24 (47.1%) *Depressive disorders included: major depressive disorder (MDD), dysthymia, minor depressive disorder,

			would make the interview infeasible; being unaware of cancer diagnoses					dysthymia, minor depressive disorder, mood disorder due to a general medical condition with major depressive-like episode or with depressive features; and mood disorder due to substances with depressive features. Time of assessment by psychiatrists while as inpatients was not otherwise specified.	mood disorder due to a general medical condition with major depressive-like episode or with depressive features; and mood disorder due to substances with depressive features.

ABBREVIATIONS: ALS: Amyotrophic Lateral Sclerosis; CPS: Cognitive Performance Score; DRS: Depression Rating Scale (InterRAI Palliative Care); DSM: Diagnostic and Statistical Manual of Mental Disorders; ECOG: Eastern Cooperative Oncology Group Performance Status; FVC: Forced Vital Capacity; HADS: Hospital Anxiety and Depression Scale; KPS: Karnofsky Functional Performance Status Scale; MDD: Major Depressive Disorder; MINI: Mini International Neuropsychiatric Interview; PHQ: Patient Health Questionnaire; PPS: Palliative Performance Scale; PHQ: Patient Health Questionnaire; RCT: Randomised Controlled Trial; SD: Standard Deviation; WHO PS: World Health Organization Performance Status

TABLE 2. 2. STUDY DEMOGRAPHICS OF INCLUDED STUDIES (N=13)

Study Characteristics	Number of Studies (n out of 13) / Study Descriptions
Study Design	
Prospective	13
Longitudinal [179-183]	5
Cross-sectional [2, 84, 184-189]	8
Country	
Saudi Arabia [189]	1
Philippine [186]	1
China (Beijing/ Hong Kong/Taiwan) [179, 184, 188]	3
United States [2, 180, 181]	3
Canada [84, 183]	2
United Kingdom [182]	1
Germany [187]	1
Denmark [185]	1
Recruitment Settings	
Inpatient only	6
General [179, 184, 189]	3
Palliative care specific [2, 183, 188]	3
Outpatient only	0
Home care only	1
General	0
Palliative care specific [84]	1
Mixed settings	4
General [180, 186, 187]	3
Palliative care specific [185]	1
Others	2
Setting not otherwise specified [181, 182]	2
Diagnoses	
Combination of malignant and non-malignant conditions [84, 189]	2
Malignant only [2, 179, 180, 182-188]	10

Combination of early and advanced cancer types [186, 187]	2
Advanced / terminal cancer (mix types) [2, 179, 180, 183, 185, 190]	6
Advanced gynaecological cancer (palliative phase) [188]	1
Lung cancer (small cell & non-small cell) on palliative chemo /radiotherapy [182]	1
Non-malignant	1
Late stage amyotrophic lateral sclerosis [181]	1
Age	
Mean age	58-70.9 among nine studies [2, 84, 183-185, 187-189] (Five studies did not report mean age)
Gender	
Male %	36.5% – 69.8% (11 studies) (One study has 0% male (gynaecological cancer study [188]; and one study did not report gender [180])
Definition of Extremely short prognoses	
1. Functional status [182-188*]	7
ECOG4 [184, 186, 187]	3
WHOPS4 [182]	1
PPS≤50 [188]	1
KPS≤40 [183, 185]	2
AKPS≤40	0
2. Survival [2, 84, 179-181, 183, 185, 189*]	8
Days prior to death [84, 179, 189]	3 (Range: 1-60 days)
Average survival (days) [2, 180, 181, 183, 185]	5 (Range: 28 to 43 days - medians used apart from one study where average is reported but the type not specified [2])
Definition of Clinically Significant Depressive Symptoms	
1. Tools [84, 179-182, 185-189Δ]	10

PHQ [180, 181, 186, 187, 189]	5
PHQ9[180, 181, 187, 189]	4
Score≥10 as major depression [180, 181, 187, 189]	4
Score 5-9 as other depressive disorders [181, 189†]	2
PHQ8≥10 (no suicide item) [186]	1
HADS [179, 182, 185, 188]	4
HADS≥11 as depression [179, 182, 185, 188]	4
HADS≥8 as borderline depression [182]	1
DRS≥3 (InterRAI PC) [84]	1
2. Criteria [2, 183, 184, 189Δ]	4
DSM [2, 183, 184, 189]	4
DSMV [189]	1
DSMIV [2, 184]	2
DSMIIIR [183]	1
ICD	0
Endicott	0
3. Conditions by DSM [2, 183, 184, 189]	4
Major depressive disorder/episode [2, 183, 184, 189]	4
Minor depressive disorder/episode [183, 184]	2
Dysthymic disorder [184]	1
Mood disorder due to general medical condition with depressive features [184]	1

Footnotes: *2 studies had both functional status / survival;[183, 185] †Rabkin et al, 2005 uses 3 or more PHQ9 items with score ≥2 as minor depression;[181] Δ1 study had both DSMV + PHQ9[189]

5.1 Prevalence of Clinically Significant Depressive Symptoms

The prevalence of clinically significant depressive symptoms in people with life-limiting illnesses and extremely short prognoses was analysed with reference to tools, diagnostic criteria and risk of bias.

5.2 Tools

1. ≥Mild or Minor Severity (PHQ8/9≥5, HADS≥8, DRS≥3)

Overall pooled prevalence of clinically significant depressive symptoms of mild/minor severity or greater (defined as: PHQ8/9≥5, HADS≥8, DRS≥3;[191-193] n = 10)[84, 179-182, 185-189] in people with extremely short prognoses (N = 905) was 50% (95%CI: 29%-70%) (Figure 2.2). There was high heterogeneity (I^2 = 97.6%).

Meta-regression found no significant differences between prevalence of depressive symptoms measured by different tools (p = 0.774). Differences in tools also did not account for the high heterogeneity among studies (Adjusted R^2 = -12.40%). Interestingly, DRS≥3 appeared to yield lower prevalence of depressive symptoms of 21% (95%CI: 17%-25%; n = 1). Removal of the prevalence data from DRS≥3 raised overall pooled prevalence to 53% (95%CI: 37%-70%) and reduced heterogeneity slightly (I^2 of 93.1%) (extremely short prognoses sample: N = 547).

2. ≥Moderate or Major Severity (PHQ8/9≥10, HADS≥11)

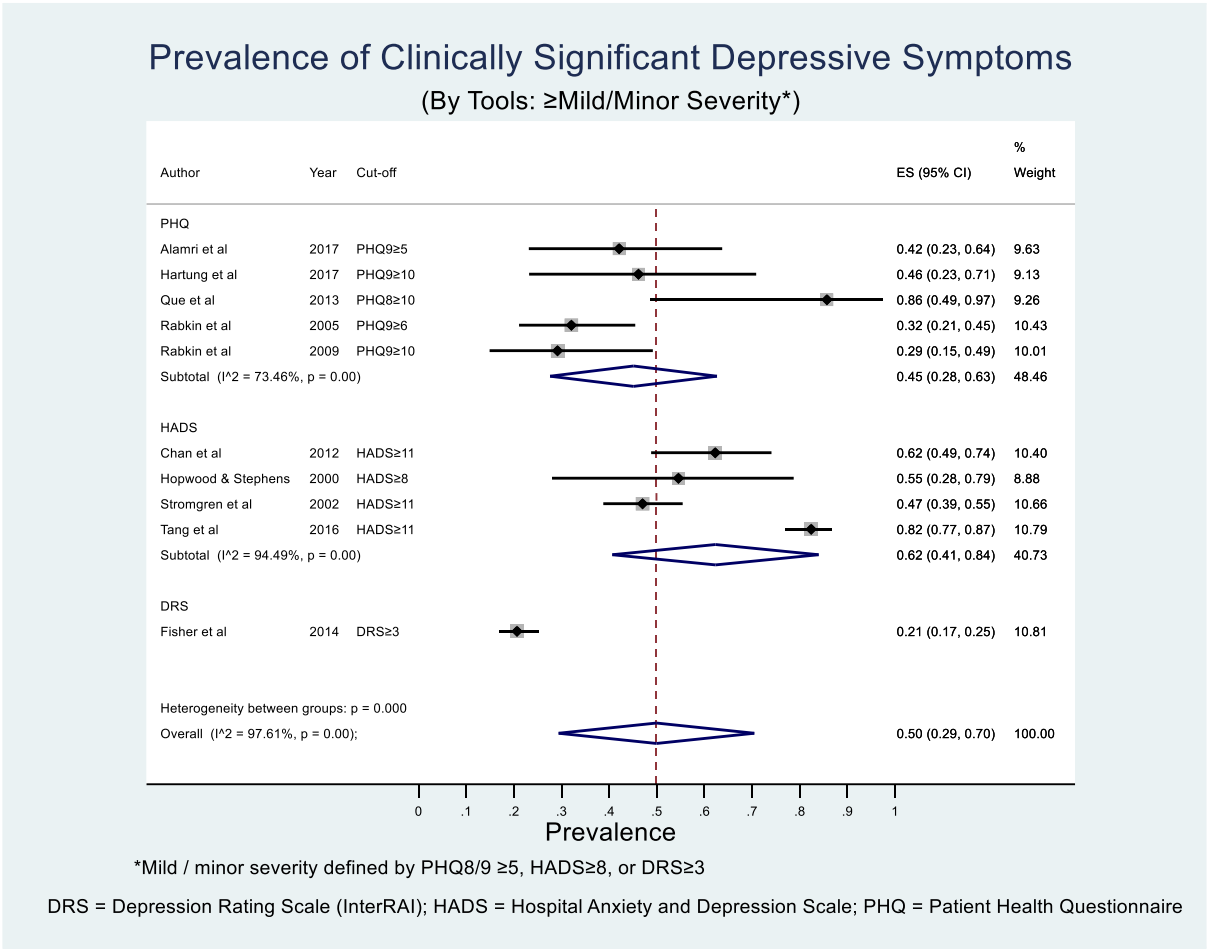
When performing sub-group analyses on depressive symptoms with the severity cut-off of moderate or more (PHQ8/9≥10 or HADS≥11;[192, 193] n = 7), pooled prevalence of clinically significant depressive symptoms in people with extremely short prognoses (N = 476) was 55% (95%CI: 37% - 74%).[179, 180, 185-189] Heterogeneity was still high (I^2 = 93.4%). (Prevalence data from DRS≥3 was not included in sub-group analysis as DRS≥3 contained both major and minor depressive symptoms).[191]

There was no statistically significant difference (p = 0.36) between pooled prevalence measured by PHQ8/9≥10 (47% [95%CI: 23%-71%]) and that by HADS≥11 (64% [95%CI: 40%-89%]), accounting for only 4.2% of the study heterogeneity in the greater or equal to moderate severity sub-group (meta-regression adjusted R^2 = 4.2%).

5.3 Common Disorders by DSM Diagnostic Criteria

Prevalence of depressive symptoms defined by common disorders through diagnostic criteria (DSMIIIR/IV/V) included:

- Major depression (Major depressive disorder / episode; n = 3):[2, 183, 189]
    - On meta-analysis, the pooled prevalence of major depression in people with extremely short prognoses (N = 308) was 10% (95%CI: 4%-16%; extremely short prognoses sample size: N = 308; Figure 2.3).
    - Heterogeneity among studies was only moderate (I^2 = 57.5%).
- Minor depression (n = 1):[183] 5% (95%CI: 2%-8%; extremely short prognoses: N = 200)



*Mild / minor severity defined by PHQ8/9 ≥5, HADS≥8, or DRS≥3

DRS = Depression Rating Scale (InterRAI); HADS = Hospital Anxiety and Depression Scale; PHQ = Patient Health Questionnaire

FIGURE 2. 2. PREVALENCE OF CLINICALLY SIGNIFICANT DEPRESSIVE SYMPTOMS IN PEOPLE WITH ADVANCED LIFE-LIMITING ILLNESSES AND EXTREMELY SHORT PROGNOSES IDENTIFIED BY DEPRESSION-SPECIFIC SCREENING TOOLS

Caption: Overall pooled prevalence of clinically significant depressive symptoms of mild/minor severity or greater (defined as: PHQ8/9≥5, HADS≥8, DRS≥3;[191-193] n = 10)[84, 179-182, 185-189] in people with extremely short prognoses (N = 905) was 50% (95%CI: 29%-70%). Heterogeneity was high (I^2 = 97.6%). For the sub-group with moderate severity or more (PHQ8/9≥10 or HADS≥11;[192, 193] n = 7): Pooled prevalence was 55% (95%CI: 37% - 74%; N = 476).[179, 180, 185-189] Heterogeneity was high (I^2 = 93.4%).

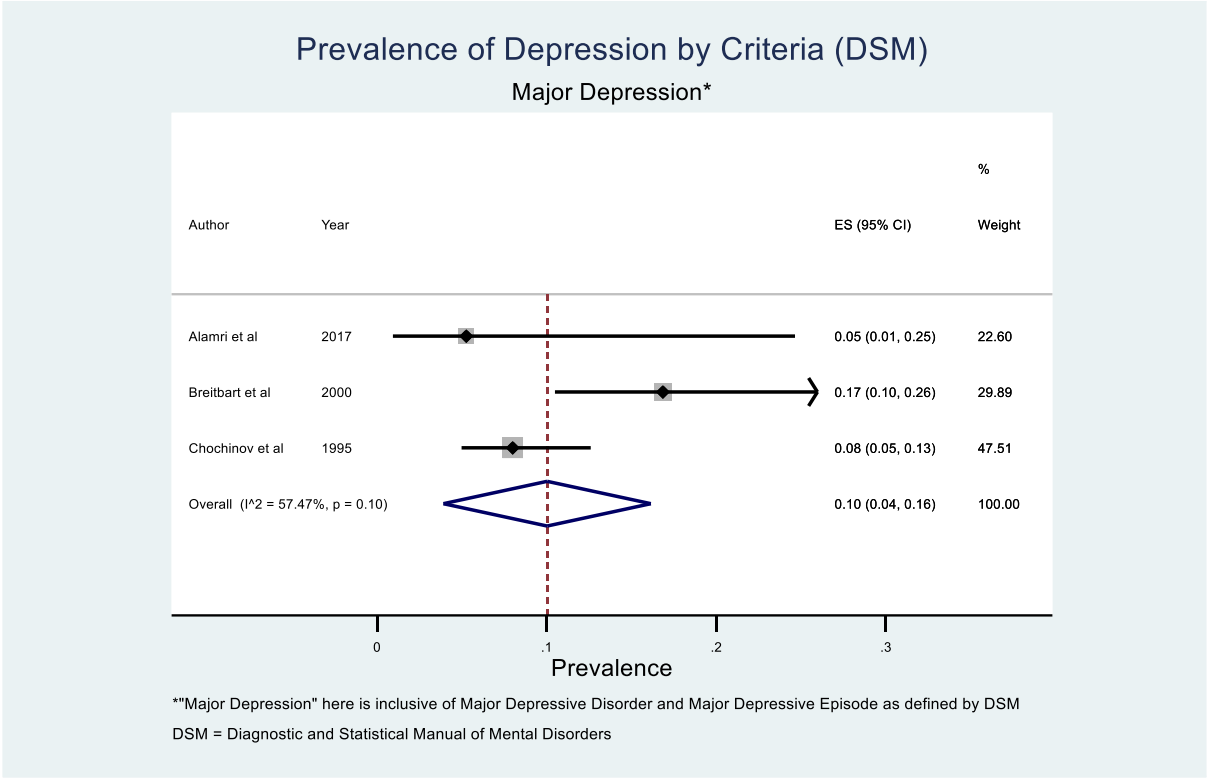


FIGURE 2. 3. POOLED PREVALENCE OF MAJOR DEPRESSION IN PEOPLE WITH ADVANCED LIFE-LIMITING ILLNESSES AND EXTREMELY SHORT PROGNOSES (N = 3; EXTREMELY SHORT PROGNOSES N = 308)

Caption: On meta-analysis, the pooled prevalence of major depression in people with extremely short prognoses (N = 308) was 10% (95%CI: 4%-16%; extremely short prognoses sample size: N = 308).[2, 183, 189]

5.4 Longitudinal Changes

In five longitudinal studies, data for longitudinal changes in prevalence of clinically significant depressive symptoms over the 3-6 months before death could be extracted in two studies.[179, 180] Tang et al (2016) reported increasing prevalence of clinically significant depressive symptoms (defined by HADS ≥11) in Chinese cancer patients as days to death approached from 44.58 % (181–365 days), 49.91 % (91–180 days), 69.44 % (31–90 days), to 82.64 % (1–30 days).[179] Rabkin et al (2009), also in the cancer population but in United States, reported a prevalence of major depression (using PHQ-9) of 0% at 3 months before death, rising to 29% in the last month of life.[180]

Two studies informed the proportion of new onset symptoms in those cases with clinically significant depressive symptoms and extremely short prognoses,

which were 36.3% [four out of 11 – Rabkin et al (2005)] and 57.1% [four out of seven – Rabkin et al (2009)].[180, 181]

5.5 Quality /Risk-of-Bias Assessment

5.5.1 Quality of Individual Studies

Seven of 13 studies did not fulfil at least 1 item of the JBI checklist (Figure 2.4). The leading source of bias (not fulfilling specified item criteria) was selection bias (Item 1-5: 21.5%), followed by attrition bias (Item 9: 15.4%), and detection/measurement bias (Item 6-7: 3.8%). No analysis bias was identified.

5.5.2 Prevalence by Low Risk-of-Bias Studies

There were only two studies found to have low risk of bias, fulfilling all nine criteria in the JBI checklist of prevalence studies. These differed in country of study and method of depression identification.[184, 185]

Despite these differences, they both had the same depression prevalence of 47%: Stromgren et al (2002) – study from Denmark using the tool HADS≥11 yielded 47% (95%CI: 39%-55%);[185] and Zhao et al (2014) – study from China using DSMIV criteria for Depressive Disorders (major & minor depression, dysthymia and mood disorders due to general medical conditions with depressive features) found 47% (95%CI: 34%-60%).[184]

5.5.3 Quality across Studies

Each domain of Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess quality across studies (described below), though the overall quality score could not be generated using the online platform for GRADE (GRADEPro) as it is not configured for systematic reviews of prevalence studies.[176, 194, 195] For risk-of-bias across studies, there were serious limitations due to the general selection bias intrinsic to researching populations with life-limiting illnesses, where participants were often excluded if they have significant cognitive impairment or frailty.

For the domain of indirectness, all studies directly addressed their research questions on the prevalence of depressive symptoms. Regarding imprecision, there is a lack of established guidance in assessing precision for meta-analyses

of prevalence studies. Assuming the use of the width of confidence intervention in the GRADE approach to assess precision, there was a relatively low precision for prevalence of depressive symptoms identified by tools (50% [95%CI: 29%-70%]), but a modest precision for that identified by diagnostic criteria, with major depression having the widest confidence interval (10% [95%CI: 4%-16%]). If precision is defined as the sensitivity and specificity of tools used, then it was relatively high across the studies, as all the tools used (PHQ, HADS and DRS) have been psychometrically tested in the palliative care or oncology settings.[191, 196-198] For inconsistency, there was high heterogeneity across studies for the prevalence of depressive symptoms by tools (I^2 = 93.4%-97.6%), but only modest heterogeneity (I^2 = 57.5%) for prevalence of depressive symptoms by diagnostic criteria for major depression.

To assess for small study effects and publication bias, studies with sample sizes of 100 or less were removed from meta-analyses. The final pooled prevalence estimates of clinically significant depressive symptoms by tools (≥ mild severity) (50% [95% CI: 8% – 92%]; I^2 = 99.4; n = 3)[84, 179, 185] and diagnostic criteria for major depression (8% [95%CI: 5.0% - 12.6%]; n = 1)[183] have not changed significantly from the estimates that included all studies. Regression (Egger's) tests of the corresponding inverted funnel plots again showed no evidence of small study effects or publication bias for the meta-analyses that included all selected studies using depression-specific screening tools (≥mild or minor severity; Egger's Coefficient: 0.87 [95%CI: -7.45 to 9.19); p = 0.815) and diagnostic criteria for major depression (Egger's Coefficient: 1.04 [95%CI: -36.12 to 38.21]; p = 0.782).

		JBI Checklist for Prevalence Studies (Items 1-9)*								
Study	Authors / Year	1	2	3	4	5	6	7	8	9
1	Alamri et al 2017	Y	Y	?	Y	N	Y	?	Y	?
2	Breitbart et al 2000	N	?	N	?	?	Y	N	Y	N
3	Chan et al 2012	Y	Y	?	Y	Y	Y	Y	Y	?
4	Chochinov et al 1995	N	?	Y	Y	N	Y	Y	Y	N
5	Fisher et al 2014	?	?	Y	Y	Y	Y	?	Y	?
6	Hartung et al 2017	?	Y	Y	?	?	Y	Y	Y	Y
7	Hopwood & Stephens 2000	N	Y	Y	N	N	Y	Y	Y	Y
8	Que et al 2013	?	?	Y	N	N	Y	?	Y	Y
9	Rabkin et al 2005	Y	?	Y	Y	Y	Y	Y	Y	Y
10	Rabkin et al 2009	N	N	N	Y	Y	Y	Y	Y	?
11	Stromgren et al 2002	Y	Y	Y	Y	Y	Y	Y	Y	Y
12	Tang et al 2016	Y	N	Y	Y	Y	Y	Y	Y	Y
13	Zhao et al 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y

*For details of Items 1-9, see: "Joanna Briggs Institute Systematic Review Checklist for Prevalence Studies" in Appendix 3

FIGURE 2. 4. RISK OF BIAS ASSESSMENT USING JOANNA BRIGGS INSTITUTE (JBI) SYSTEMATIC REVIEW CHECKLIST FOR PREVALENCE STUDIES[173, 174]

CAPTION: Seven out of 13 studies did not fulfil at least 1 item of the checklist. Only two studies were found to have low risk of bias, fulfilling all nine criteria. The leading source of bias (not fulfilling specified item criteria) was selection bias (Item 1-5: 21.5%), followed by attrition bias (Item 9: 15.4%), and detection/measurement bias (Item 6-7: 3.8%). No analysis bias was identified.

6. DISCUSSION

6.1 High Prevalence of Clinically Significant Depressive Symptoms in Extremely Short Prognoses Setting

This evidence synthesis found high prevalence (one in two individuals) of clinically significant depressive symptoms in people with extremely short prognoses.

The duration of a median survival of one month (indicated by the functional scores of KPS ≤ 40 or ECOG 4) with the upper limit of two months was used to differentiate individuals with extremely short prognoses from others with

advanced life-limiting illnesses. This is an important distinction as this time period is the time during which frailty and symptomatology of the terminal illnesses (e.g., fatigue, delirium and inability to swallow) significantly escalates.[47, 48, 199] This hinders effective depression assessment and management. This extremely short life-expectancy period makes the conventional depression interventions unlikely to be successful due to their slow onset-of-actions, and supports the consideration for alternative rapid-onset interventions such as methylphenidate or ketamine.[10, 112, 200]

The prevalence of clinically significant depressive symptoms in advanced life-limiting illnesses using HADS score ≥11 have been reported in a systematic review to be around 29%.[14] This review adds to the data by finding a higher pooled prevalence of 50% in the sub-group with extremely short prognoses using depression-specific tools. If only studies with HADS score ≥11 were considered, an even higher overall pooled prevalence of 64% resulted, including the 47% from the low risk-of-bias study.[185]

Meanwhile, the prevalence of combined depressive disorders in the general advanced illness population using diagnostic criteria has been reported to be 25% in another systematic review.[12] As seen in this review, this is lower than the corresponding prevalence of 47% found using diagnostic criteria in people with extremely short prognoses.[184] The higher prevalence of clinically significant depressive symptoms in those with extremely short prognoses is further supported by the findings of longitudinal studies by Tang et al (2016) (included in this review) and Seow et al (2011), where both studies reported increases of 33% and approximately 10% respectively in prevalence of clinically significant depressive symptoms in the last six months of life.[47, 179]

Reasons for high prevalence of clinically significant depressive symptoms in people with advanced life-limiting illnesses and extremely short prognoses are likely multi-faceted. In addition to individuals having the stressors of advanced life-limiting illnesses and associated adjustment issues, inadequacy of recognition, assessment, and management of these symptoms during life-limiting illnesses at earlier stages may be a factor. Studies reveal around 40% of clinicians treating people with advanced life-limiting illnesses do not regularly

screen or assess for depressive symptoms, with as low as 7% of the depressed cases being recognised and up to 70% of affected individuals receiving inadequate interventions.[67, 68, 147-149, 184] There is intrinsic difficulty in assessing depressive symptoms in individuals whose advanced life-limiting illnesses might mimic depressive symptoms, as well as challenges in providing interventions likely to be effective in time.[35, 112] Further barriers to suboptimal recognition, assessment and management include: clinicians' fear of distressing patients, especially given the stigma associated with psychiatric diagnoses;[13, 115] lack of awareness and skills to detect and manage depression;[36, 67-69, 76, 147, 151-154] perceived lack of resources such as time,[67, 68, 155] acceptable assessment tools and access to mental health services;[67, 71-74, 78, 115, 156] beliefs that depression is 'normal';[115, 155] and that screening & interventions are likely to be futile in this context.[36, 76, 151, 157] It is possible that addressing these barriers might lead to an earlier detection and management of depressive symptoms in people with advanced life-limiting illnesses, which may subsequently lower prevalence when prognoses are extremely short.

Meanwhile, a significant proportion (36%-57% from Rabkin et al (2005) and Rabkin et al (2009) in this review[180, 181] of individuals with advanced life-limiting illnesses and extremely short prognoses were experiencing clinically significant depressive symptoms for the first time. This is also supported by the findings of a trend for building prevalence as death approaches.[179, 180] Given the limitation of having only small number of studies with small sample sizes, these findings need to be interpreted with caution. The findings should not be perceived as definitive but hypothesis generating. The exact prevalence of new-onset cases needs to be further studied. Nonetheless, one might also ponder on the underlying drivers for having a substantial proportion of new cases of depressive symptoms in the last weeks to days of life. It may be possible that the pathological processes of the advanced life-limiting illnesses themselves such as brain metastases or hypercalcemia cause depressive symptoms.[190] Other potential drivers for new-onset depressive symptoms may be: the associated distressing symptoms and functional limitations that are often more marked towards the end-of-life due to disease progression;[47, 179, 182, 201] the associated grief & hopelessness;[43] loss of dignity;[101, 202] concerns about social

relationship (e.g. perceived lack of support or fear of being a burden to others);[179, 183, 201] and existential distress.[202] It would be instructive to see whether targeting these issues decreases incidence of depressive symptoms in people with extremely short prognoses in future studies.

6.2 Methods of Defining Clinically Significant Depressive Symptoms

The construct of clinically significant depressive symptoms is an interesting one. It encompasses depressive disorders diagnosed by the conventional diagnostic criteria. It also includes sub-syndromal depression where depressive symptoms are severe enough to fulfil certain thresholds set by various depression-specific screening tool but cannot be diagnosed as specific depressive disorders using diagnostic criteria. In fact, the sole use of diagnostic criteria in assessing for depressive symptoms in the extremely short prognoses setting has its limitation. There may not be enough time for specific depressive disorder (e.g. 2 weeks for major depressive disorder)[4] to be established as the affected individual might not live long enough. Assessing the prevalence of depressive symptoms using only diagnostic criteria will, therefore, underestimate the true prevalence of these symptoms. The addition of using validated depression-specific screening tools in the palliative care setting to identify individuals with clinically significant depressive symptoms would overcome the issue of missing individuals with sub-syndromal depression. Nonetheless, the use of depression-specific tools does come with the intrinsic shortfall of “false-positivity”. As these tools are often used at a particular time point, if they are used as an indirect measurement for specific depressive disorder (e.g., major depression), they might over-estimate the prevalence of such. Perhaps a better way to perceive the use of depression-specific screening tools is not to use them to predict for certain depressive disorders. Rather, these tools have the value in identifying people who have clinically significant depressive symptoms at a certain time point that requires further assessments and interventions. This would help identify and address people with clinically significant sub-syndromal depression who might otherwise be missed by the treating clinicians.

When determining prevalence of depressive symptoms by depression screening tools, the myriad of tools used was noteworthy. Among these,

relatively few have been validated for use in the palliative care setting. These include: HADS, Single and Two Items Questions ("Are you depressed?" +/- "Have you lost interest in activities?"), Visual Analogue Scale, Edinburgh Postnatal Depression Scale, and Beck Depression Inventory-Short Form.[203] The current study identified three tools that were used in people with life-limiting illnesses and extremely short prognoses: Patient Health Questionnaire 8/9 (PHQ 8/9), HADS and Depression Rating Scale (DRS - InterRAI PC). This review and meta-analysis did not observe any statistical differences between them. This is consistent with the findings by Cameron (2008) and Hansson et al (2009) that demonstrated similar prevalence of depressive symptoms generated by HADS and PHQ-9 with overall convergent validity between the two tools, though there was a lack of convergence between the severity cut-offs.[192, 193] However, it is possible that this study was insufficiently powered with only a modest number of studies using tools (n = 10). Particularly, the one study that used DRS seemed to have yielded the a low prevalence estimate.[84] The underlying reason might be due to the construct of DRS. DRS was originally designed to detect depressive symptoms in nursing home residents, for whom assessing patients face-to-face using psychiatric interviews or self-reported depression-specific tools might be impractical.[191] Its scoring depends on the daily observed standardised mood and behavioural item data collected in the Resident Assessment Instrument, the Minimum Data Set.[191] Different from PHQ-8/9 or HADS, it only contains three depression-specific items (sad facial expression, tearfulness, and observed negative statements by residents [passive suicidal ideation]). Four other items are less depression-specific (anger & irritability, expressions of fears, repetitive health complaints; and repetitive anxious concerns).[191] Therefore, there is a possibility that DRS under-recognised depressive symptoms in patients who had other depressive symptom items included in PHQ-8/9 or HADS but did not have depressed or teary affect, leading to a lower prevalence estimate. The comparison and feasibility of these tools for the use of detecting clinically significant depressive symptoms in people with extremely short prognoses warrant further investigation.

In contrast, when exploring the prevalence of depressive symptoms using diagnostic criteria (gold-standard) for specific depressive disorders, the prevalence of major and minor depression represented a relative minority. Major and minor depressions accounted for only 10% and 5% respectively of those with extremely short prognoses and clinically significant depressive symptoms. This reflects the observations that clinically significant mood disturbances are prevalent (around 40%) but major depression is relatively uncommon in the general cancer or terminal settings.[204, 205] In fact, its prevalence might not increase as death approaches.[205] Nonetheless, the pooled prevalence of combined depressive disorders (major & minor depression, dysthymia and mood disorders due to general medical conditions with depressive features) found in this review was high, at 47% by Zhao et al (2014)[184]. This raises the possibility that much of the clinically significantly depressed individuals with extremely short prognoses may not be diagnosed with major or minor depression, but rather, be labelled as other disorders with depressive features (e.g. adjustment disorder).[190] Interestingly, the composite prevalence of various depressive disorders for people with extremely short prognoses of 47% seemed to equate to the prevalence of depressive symptoms defined using screening tools (as seen in the results of the low-risk-of-bias studies and the pooled prevalence of 50%-55% in meta-analyses using tools).[184, 185] This raises the possibility that, in those with extremely short prognoses, one can use depression screening tools such as HADS or PHQ to estimate the combined prevalence of various depressive disorders (and therefore the burden of depression). This would avoid the need to undergo extensive psychiatric interviews as required by the diagnostic criteria for patients for whom these interviews might be too burdensome and thus not be feasible. This too warrants future study. Importantly, these screening tools should not replace diagnostic criteria in diagnosing depressive disorders.[10] Rather, these screening tools are means to help clinicians identify individuals with clinically significant depressive symptoms needing interventions.

6.3 Limitations and Strengths

The predominant types of risk of bias across studies in this review, consistent with the other similar systematic reviews exploring the prevalence of depressive symptoms in advanced life-limiting illnesses, were selection and attrition (non-responder) biases.[12, 14] A significant proportion of participants with extremely short prognoses were excluded due to their being significantly cognitively impaired or too frail to undergo study assessment. This is an intrinsic challenge to depression research in the terminally ill. In fact, assessment of depressive disorder is contentious for those with significant cognitive impairment or dementia, marked by a wide range of prevalence of depressive symptoms, and hence were excluded in this systematic review.[206-208]

Another limitation of this review is that studies that used general symptom measurement scales with non-specific depression measurement such as the Edmonton Symptom Assessment System Depression Score (ESAS) were excluded.[46, 47] This was to ensure measurement accuracy. However, prevalence of depressive symptoms in people with extremely short prognoses captured by ESAS in Seow et al, 2011 (36%) and Liu et al, 2013 (41.7%) were consistent with results of this systematic review.[46, 47] This raises the possibility that ESAS may be a feasible screening tool for depressive symptoms in people with extremely short prognoses.

Similar to other systematic reviews reporting prevalence of depressive symptoms in palliative care, this systematic review is limited by the high heterogeneity of the included studies.[12, 14] Due to the small number of studies included (n = 13) and many studies having a combination of variables (e.g. a combination of malignant and non-malignant diseases or mixed recruitment settings), extensive investigation of potential moderators that account for heterogeneity using meta-regression cannot be performed with statistical validity. Nonetheless, one can postulates that the majority of heterogeneity is contributed by the same factors listed in other similar systematic reviews: the various populations studied, assessment methods and depression definitions.[12, 14]

The results reported by this review represents possibly the largest number of people with extremely short prognoses (N = 1245) in the current literature. This review utilised inclusive search strategies to include the broader population of advance life-limiting illnesses that would not necessarily have been referred to palliative care, as well as both malignant and non-malignant disease. However, there is a relative lack of representation of studies focusing on non-malignant disease. This is because most such studies did not include a measure of functional status, especially later in people's disease trajectory. Additionally, many studies did not report the prevalence findings of malignant or non-malignant diseases separately. Therefore, comparison of prevalence estimates between studies with malignant versus non-malignant disease was not possible.

An important limitation of this review is the inclusion of studies with small sample sizes into the meta-analysis, introducing the risk of small study effects and publication bias.[209-211] Nonetheless, funnel plots and Egger's regression tests have demonstrated the lack of small study effects and the removal of studies with sample sizes of 100 or less have demonstrated comparable findings.[209] Perhaps, in this context, a robust estimation of prevalence would be achieved through including all available evidence as limiting studies due to small study size may introduce subjectivity to the final result.[211] However, the lack of sample size in individual studies have contributed to the overall limited precision of the prevalence estimates. This is indicated by the wide confidence intervals of the prevalence data.

A strength of this review is that the prevalence of clinically significant depressive symptoms has been explored by considering various methods of detection (utilising depression-specific screening tools and different diagnostic criteria through psychiatric interview). This ensures that the pooled prevalence better reflects the overall global burden of depressive symptoms experienced by this sub-population, as assessing such prevalence by solely using diagnostic criteria may underestimate its prevalence: firstly, it excludes detecting clinically significant depressive symptoms that would otherwise not fulfil the diagnostic criteria of that specific depressive disorder(s) studied;[204] and secondly, it eliminates up to approximately 80% of patients with extremely short prognoses

who find the assessment of diagnostic criteria using psychiatric interviews too burdensome due to their cognitive impairment or frailty (contributing to the majority of the selection bias seen in this systematic review).[2, 14, 183] However, despite best intentions to differentiate grief reactions from pathological depressive symptoms, the intrinsic limitation of using these screening tools to define depressive symptoms is such that normal anticipatory grief may not be entirely excluded from pathological depressive disorders.[203, 212]

Another major strength of this study is that this is one of the few reviews with meta-analysis of prevalence that uses formal guideline to critically appraise individual studies (JBI Systematic Reviews Checklist for Prevalence Studies) and across studies (GRADE approach), for the first guideline established to appraise individual prevalence studies was only published in 2017.[173-176] For quality assessment across studies, GRADE approach has been frequently utilised for meta-analysis of cause-and-effect and diagnostic tools.[176, 194, 213] However, it has yet to be adapted for the use of assessing prevalence studies.[195] Nevertheless, this systematic review uses the general principles of the GRADE approach to perform quality assessment across studies.

6.4 Implications

The findings of the increase in prevalence as death approaches with up to half of the people with extremely short prognoses having clinically significant depressive symptoms have major implications for clinical practice, policy makers & funders, and future research.

6.4.1 Implications for clinical practice

There is a need for some forms of systematic processes (e.g. regular screening for depressed mood after first contact with palliative care services) to increase clinicians' awareness of potentially depressed individuals, as the affected individuals might be reluctant to report symptoms of depression due to social stigma.[13, 14, 67] Patients and families may need to be encouraged to talk about their mood by clinicians, and certain components of the depression screening tools might be helpful to act as prompts (e.g., using PHQ-9 to ask about anhedonia).

Emphasis must be placed on clinicians to not neglect patients' concerns of depressed mood in the context of having extremely short prognoses as 'normal reactions' to the dying process. Clinicians need to be aware that there is a high likelihood of these patients suffering from depressive symptoms that significantly impair their quality-of-life. These depressive symptoms (sub-syndromal depression) may not meet the diagnostic criteria of various depressive disorders in the setting of extremely short prognoses. These disclosures from patients, therefore, need to be thoroughly explored and addressed, with the expression of depressive symptoms encouraged and de-stigmatised[13]. Individuals with sub-syndromal depression may still benefit from various psychological support interventions to prevent more severe depressive symptoms and disorders from developing.[10]

6.4.2 Implications for policy makers and funders

The high prevalence of clinically significant depressive symptoms in this subgroup of extremely short prognoses necessitate the treating clinicians to be trained and empowered for timely assessment and management of depressive symptoms, justifying the prioritisation of healthcare resources towards this area. The clinical culture needs to be one that offers supportive environment to staffs engaging with depressed patients (e.g., allowing extra time in clinic for depression assessment, offering de-briefing sessions for staffs). Integration between palliative care and psychiatry may improve the tendency of under-recognition of depressive symptoms, leading to better depression care.[150, 214, 215] Public health interventions aiming at improving public awareness of mood health at the end-of-life, de-stigmatising depressive symptoms and encouraging open discussion are also required.[13]

6.4.3 Implication for future research

This review highlights the needs for further research in people with advanced life-limiting illnesses and extremely short prognoses as studies focusing on this sub-population as their primary objectives are lacking. The wide confidence intervals of prevalence estimates found in this study reflects the lack of any agreed nation or international criteria for referral to hospice / palliative care services, and the relatively poor estimation of people's prognosis by many

clinicians. Importantly, this systematic review and meta-analysis forms an important first step to create a platform for more uniform population eligibility definitions for future, larger studies. The validity and acceptability of using functional score as prognostic indicators for extremely short prognosis in non-malignant diseases needs to be further explored.

For depression research in this sub-population, identifying a feasible and acceptable screening tool and assessing the benefits of implementing screening is vital. The optimal method of assessing depressive symptoms when there may be insufficient time for patients' symptoms to fulfil certain components of the conventional diagnostic criteria (e.g., the 2 weeks duration for major depressive disorder in DSM)[4, 23] and the feasibility and acceptability of the substitute approach need further exploration (i.e., Endicott Criteria).[81] Clinicians' perspectives on assessing and managing depression in this context, as well as the corresponding views from patient and their families also require study.

7. CONCLUSION

Clinically significant depressive symptoms (including sub-syndromal depression) are common in people with advanced life-limiting illnesses and extremely short prognoses (approximately 50%).

Clinicians caring for people with extremely short prognoses need to be proactive in the recognition and assessment of these symptoms to allow for timely administration of appropriate interventions. Much research is required to establish effective assessment and management strategies in this field.

CHAPTER 3 – EFFECTIVE INTERVENTIONS FOR CLINICALLY SIGNIFICANT DEPRESSIVE SYMPTOMS IN PEOPLE WITH EXTREMELY SHORT PROGNOSES

1. PREFACE

Chapter 2 describes the burden of clinically significant depressive symptoms in people with extremely short prognoses, finding one in two individuals with advanced life-limiting illnesses in the last days to weeks of life experienced clinically significant depressive symptoms needing interventions. Chapter 3 builds on this to explore what interventions are effective against clinically significant depressive symptoms in this context of extremely short prognoses.

This chapter is the expanded version (to allow for detailed discussion) of the following letter to editor that reported a systematic review of the international RCT literature, published in 2022 in *Journal of Palliative Medicine* (Appendix 4), edited and formatted to conform to the thesis guidelines:

Lee, W., Pulbrook, M., Sheehan, C., Kochovska, S., Chang, S., Hosie, A., Lobb, E., Draper, B., Agar, M. R., & Currow, D. C. (2022). Evidence of Effective Interventions for Clinically Significant Depressive Symptoms in Individuals with Extremely Short Prognoses is Lacking – a Systematic Review. *Journal of Palliative Medicine*, **25**(3), 341-342. (Citations: 2; Altmetric: 2)

2. INTRODUCTION

There exist many systematic reviews of non-pharmacological and pharmacological interventions for clinically significant depressive symptoms for people with advanced life-limiting illnesses. Some examples include non-pharmacological therapies such as cognitive behavioural therapies, life review therapy, music therapy, and pharmacological interventions such as typical antidepressants.[95, 98, 112, 216-224]

However, when caring for the sub-group of patients with extremely short prognoses, clinicians may feel a sense of therapeutic nihilism (as reported by Porche et al [2014] and in Chapter 4).[67] The frailty of these individuals, their symptom burden, and prevalence of cognitive impairment often interfere with the use of conventional depression interventions (e.g., due to inability to

swallow oral antidepressants, fatigue, and breathlessness).[48, 199] In fact, one retrospective case note analysis of terminally ill patients (n >1000) found that more than 70% of palliative patients with depression did not receive potentially effective therapy, and those who received antidepressants were nearly always under-dosed.[149]

Despite the high prevalence of clinically significant depressive symptoms in people with advanced life-limiting illnesses and extremely short prognoses (as reported in the previous chapter), systematic review evidence for effective interventions is currently lacking.

By determining what effective interventions are available, it may help equip clinicians facing this challenging management issue at the end-of-life with means to improve depression for those dying with it.

3. AIM

To determine the effective pharmacological and non-pharmacological interventions for clinically significant depressive symptoms in people with extremely short prognoses (median survival of ≤ 4 weeks with absolute cut-off of < 2 months) suffering from advanced life-limiting illnesses, as indicated by survival or functional status data (AKPS ≤40 or equivalent).

4. METHODS

4.1 Design & Protocol Registration

This systematic review was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[170] The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42019125119).

4.2 Search Strategy

The electronic databases of MEDLINE (OVID), PsycINFO, Embase, CINAHL, and CareSearch (CareSearch filter utilised via PubMed) were searched systematically for studies published between January 1994 and March 2020

(last searched 11 March 2020). The search was limited to the last 26 years because DSM-IV was aligned with ICD-10 in 1994.[26]

The search strategy included search terms in the domains of [Palliative Care or Advanced Life-Limiting Illnesses] AND [Randomised Controlled Trials] AND [Depression]. These terms were used initially in MEDLINE (OVID), then adapted for other electronic databases accordingly (see Search Strategy in Appendix 5).

Inclusion criteria for studies were: adults (≥ 18 years of age) with advanced life-limiting illnesses with extremely short prognoses, defined by either survival data (absolute survival < 2 months) or functional status indicative of median survival of one month (equivalent to AKPS ≤ 40 or ECOG 4); clinically significant depression/depressive symptoms, defined by a validated tool or a depressive disorder defined by diagnostic criteria (DSM or ICD or equivalent); any prospective randomised controlled trial design with any setting of care, including clinically significant depressive symptoms in the randomisation process; and various non-pharmacological and pharmacological interventions.

Excluded studies were those not peer-reviewed (e.g., theses); studies with no validated method of assessing depressive symptoms; studies using measures not specific to depression (e.g., Edmonton Symptom Assessment Scale); Studies on the effect of health service delivery (e.g., introducing palliative care services to respiratory clinic); systematic reviews and meta-analyses; case studies, opinion papers, editorials, study protocols or guidelines; and studies without the changes of depression scores pre and post intervention as an outcome of interests.

Manual selection for adult, human and English-language studies was performed without the use of filters to minimise the risk of missing articles due to delayed coding issues. The reference lists of relevant systematic reviews and meta-analyses were hand-searched for eligible studies.

4.3 Study Selection

Search results were imported into Endnote X9.2 for duplicate removal, and subsequently exported to Covidence for title-, abstract- and full-text screenings.[171, 172]

Each study was reviewed by both the primary investigator (WL) and a reviewer from the alternative reviewer group (MP, CS, EL, AH, SC, MA, SK) with reasons for exclusions at full text review documented. A third independent reviewer (EL) was involved in resolving conflict.

4.4 Data Extraction

Data extracted from individual studies included: country; eligibility of sampled population; settings; diagnoses; participant demographics; sampling method; definition and number of participants with extremely short prognoses; depression definition, assessment timing and method; intervention description according to the template for intervention description and replication checklist and guide (TIDieR); depression scoring method with baseline and post-intervention scores; quality of life score (if available); definition and prevalence of positive response; outcome for effectiveness in participants with extremely short prognoses.

Quality and risk of bias assessments were performed using Scottish Intercollegiate Guidelines Network Methodology Checklists for controlled trials (individual studies)[225] and the principles of Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (across studies).[175, 176]

The primary investigator (WL) extracted data from all included studies. Alternative reviewers (from the co-author team) checked the validity of extracted data and independently performed quality/bias assessment of studies by randomly selecting studies using a random number generator.

4.5 Data Synthesis

Estimates of the standardised mean differences and the associated 95% confidence intervals of various interventions were planned to be synthesised using a random effects meta-analysis model. Funnel plots were planned to investigate small study effects due to possible reporting biases or heterogeneity.

5. RESULTS

There were 6107 studies identified through electronic databases (Figure 3.1). After removing 1935 duplicates, 4172 studies were screened against titles and abstracts, and 242 articles underwent full-text screening.

The primary reasons for study exclusion from the full-text screening of the 242 articles were that they did not contain the target population (n = 100; 41.3%), or the study design of interest (n = 94; 38.8%). Other reasons for exclusion were that they were conference abstracts/posters (n = 26; 10.7%), duplicates (n = 21; 8.7%), and in languages other than English (n = 1). No study was excluded due to the described intervention relating to health service delivery.

Of the 100 RCTs excluded due to study population ineligibility: 55 did not include extractable data for the sub-group with extremely short prognoses; 11 did not have clinically significant depressive symptoms in their inclusion criteria; and 33 were excluded for both reasons. One study was excluded due to having a dementia population in which the diagnosis of depressive disorders is contentious (categorised as “Other – Wrong Population”).[206, 208]

Of the 94 studies excluded because of their study design, most were systematic reviews or meta-analyses (n= 83; 88.3%). The rest were literature reviews (n = 2; 2.1%), letters to editor / commentary (n = 5; 5.3%), protocol manuscripts (n = 2; 2.1%), and theses (n = 2; 2.1%).

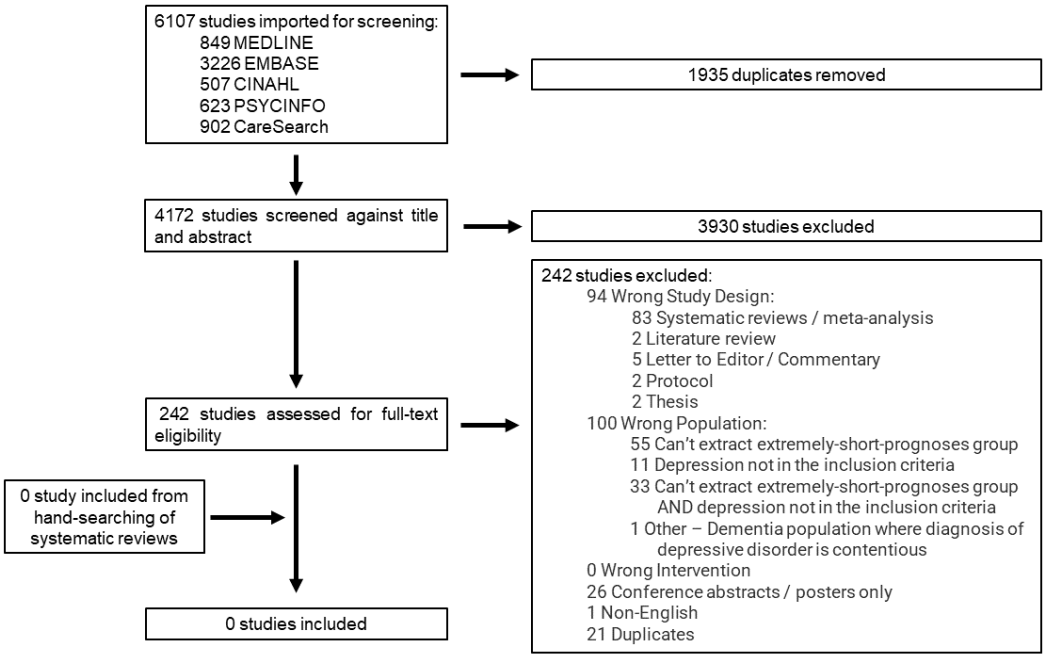


FIGURE 3. 1. PRISMA FLOW DIAGRAM

Of 6107 studies identified initially and 242 assessed for full-text eligibility, none was identified to be eligible for analysis.

6. DISCUSSION

This is the first systematic review of the literature on interventions for clinically significant depressive symptoms in people with advanced life-limiting illnesses and extremely short prognoses. While it identified numerous RCTs and systematic reviews for depression interventions for people with advanced life-limiting illnesses overall, no study directly informed the degree of effectiveness and tolerance of any intervention in people with extremely short prognoses. Thus, this review's most important contribution is its identification of the absence of RCT evidence for depression interventions in this specific context.

There is an urgent need to build the evidence for depression interventions in people with extremely short prognoses, given the distinct needs of this cohort - frailty, symptom burden, and complications associated with having a terminal illness.

6.1 Clinical, health service & policy considerations

This review demonstrates that clinicians do not have RCT data that informs them of non-pharmacological and pharmacological depression interventions in patients with extremely short prognoses. As such, all interventions may be considered experimental in nature with unknown efficacy and unknown risks of harm.[64] In the absence of evidence, clinicians should consider informing patients and their families of the uncertainty of these interventions' effectiveness and harms before they are commenced. After any such interventions are commenced, patients' responses to these interventions should be diligently monitored to ensure that the benefits outweigh the harms.[64]

The lack of RCT data to inform any effective intervention for clinically significant depressive symptoms in the context of extremely short prognoses further supports the need for clinicians to consider depression treatment in the setting of low-burden clinical trials for affected individuals. This may enable more rapid improvement in patients' outcomes, facilitate access to interventions that might otherwise not be accessible, and better monitoring of the treatment response of the interventions (efficacy and harms).[64, 226] Not only might the conduct of clinical trials in the palliative care setting lead to better patient outcomes, but evidence suggests that patients and their families receiving palliative care welcome the possibility of clinical trials.[226-228] Arguably, patients' access to clinical trials should not be restricted simply because of their extremely short prognoses. Given the uncertainty of the efficacy and tolerance of the current depression intervention in this setting and that extrapolation of data from other populations might not be appropriate, patients and their proxies might be highly receptive to clinical trial participation.

6.2 Research/trialist considerations

Researchers undertaking intervention studies in patients with advanced life-limiting illnesses often struggle with low recruitment and retention rates due to the advanced nature of participants' illnesses.[63, 229] The difficulty in conducting clinical trials can be compounded by the fact that clinicians often under-recognise and under-treat depressive symptoms in people with extremely short prognoses.[67, 69, 149] It is crucial for researchers involved in depression research

with people that have advanced life-limiting illnesses to consider explicitly identifying and describing patients with extremely short prognoses and clinically significant depressive symptoms in their studies.

The main reasons for RCTs being excluded in this review were the: 1) lack of inclusion of clinically significant depressive symptoms during the randomisation processes; and 2) inability to extract data for those with extremely short prognoses (due to this target population being excluded or the study not reporting the required survival data or functional status of extremely short prognoses).

Whether the inclusion criteria for this review of life expectancy (median survival of ≤ 4 weeks) and the need to include validated clinically significant depressive symptom diagnoses were too stringent are reasonable questions. However, given the assessment and management of clinically significant depressive symptoms in this sub-population with extremely short prognoses pose challenges distinct from those with longer prognoses (including the difficulty in differentiating the symptoms of depression from those of terminal illnesses, the lack of time for interventions to work, and the risk of intolerance of these interventions by patients), these stringent eligibility criteria were deemed necessary to generate meaningful and scientifically robust evidence.[10]

Perhaps, the more important question is: how can depression research in the context of extremely short prognoses be made more feasible? Due to the frailty of these participants and the risk of adverse events, researchers might need to consider an individualised dose-titration approach to their study intervention to minimise the risk of harm while attempting to make the intervention very brief.[44, 230-232]

Another consideration is the choice of study design. The use of conventional RCT study design might not be feasible for many depression intervention trials in those with extremely short prognoses due to the potential for poor recruitment and high attrition rate, resulting from the participants' frailty, other life priorities, and the risk of disease progression.[63, 229] Studies may face the risk of being underpowered. The heterogeneous nature of end-of-life participants in terms of

life-limiting illnesses and responses to treatment also reduces the chances of finding a statistically significant effect if the study results are analysed as a collective cohort, as often done in the conventional RCT design.[63] Therefore, researchers need to consider alternative study designs.

An n-of-1 study design may be of use for study interventions that are rapid in their onset and offset actions and do not alter the underlying depression conditions (e.g. benzodiazepines, antipsychotic +/- methylphenidate, or ketamine).[233-235] Nonetheless, the N-of-1 design is not useful for the typical antidepressants and many non-pharmacological interventions due to their gradual effects and prolonged course, necessitating a long cycle time that is unrealistic in these patients.[233] The use of Bayesian adaptive design with Response Adaptive Randomisation, which increases allocation ratios to the more promising intervention arms to improve the probability of success, may reduce the chance of under-powering a study.[236, 237] However, it requires statisticians and research infrastructure with Bayesian expertise. Using non-RCT methods such as high-quality prospective case-control studies or modifying Naranjo criteria (a systematic method that gives the probability of a causal relationship between a drug and the adverse event) to imply some causal relationship for depression interventions could also be considered.[238] Adding a qualitative component to quantitative research may also capture a treatment effect that might not be identified due to the small sample size.[63]

Additionally, it might be valuable to discuss specific reasons for excluding various depression intervention RCTs in this review for the development of these studies in the context of extremely short prognoses.

6.2.1 Non-pharmacological interventional studies

Numerous non-pharmacological interventions (> 10 types) have been studied in people with both cancer and non-cancer advanced life-limiting illnesses, ranging from conventional psychotherapies such as cognitive behavioural therapies[232, 239-242] and existential therapies[44, 102, 220, 221, 243-251] to complementary interventions such as massage,[34, 252-260] music[98, 222, 261-267] and art therapies.[268-273]

While non-pharmacological intervention studies often require participants to be capable of engaging with the therapy, hence excluding people with extremely short prognoses due to frailty, researchers need to consider adapting these interventions to be briefer and less burdensome. Apart from a few psychotherapy interventional studies,[44, 232, 247, 249, 250] most psychotherapy trials had an intervention duration that outlasted the life expectancy of people with extremely short prognoses. Researchers can consider shortening the course of depression interventions to include this subpopulation with significant frailty.[44, 232, 247, 249, 250]

Few non-pharmacological intervention studies defined clinically significant depressive symptoms as specific depressive disorders using DSM/ICD diagnostic criteria. Most studies defined these symptoms using depression-specific assessment tools and even generic well-being or quality-of-life scores. Therefore, any synthesised evidence of these trials may reflect their effectiveness in relieving the total burden of depressive symptoms rather than their effectiveness in treating specific depressive disorders. Researchers need to consider the use of diagnostic criteria to identify clinically significant depressive symptoms in this cohort, which might be challenging due to the overlap of symptoms of terminal illnesses with the somatic symptoms of depression.[13] A possible option may be to use the substitutive approach of diagnosing depressive disorder (e.g., Endicott Criteria) to facilitate the identification of significant depressive disorder in the context of terminal illnesses.[81]

6.2.2 Pharmacological interventional studies

In contrast to the non-pharmacological intervention RCTs, pharmacological intervention RCTs usually identified clinically significant depressive symptoms using diagnostic criteria, including them in the randomisation process.[107, 124] Nonetheless, they lacked extractable data for the extremely short prognoses sub-group that could be used to inform the effectiveness of the interventions.

Interestingly, apart from the typical antidepressants, which have a relatively slow onset of action (and hence possibly low utility in those with extremely short

prognoses), some trials investigated pharmacological interventions that might have a faster onset of action: methylphenidate [122]; benzodiazepine;[274] ketamine;[275] and psilocybin.[45, 276] These interventions may be promising. Future development of these interventional trials should consider including participants with extremely short prognoses by, for example, not setting an upper limit of age for inclusion or including the low functional status equivalent of KPS 40 or less or ECOG 4.

Should the inclusion of this frail sub-population cause concerns because of a perception that they may not tolerate the tested pharmacological intervention, researchers could consider the use of individual dose-titration designs to minimise the risk of harms for these participants, rather than excluding them.[230]

Lastly, depressed people with extremely short prognoses have several characteristics that can increase their vulnerability as research participants. They often have associated cognitive impairment, co-existing symptom burdens, and clinically significant depressive symptoms, which can all impair their capacity to advocate for their wishes and make decisions concerning research participation.[48, 277-279] Nonetheless, despite their potentially impaired capacity, there is evidence to suggest that a significant proportion of these individuals wish to participate in research but require additional support.[227, 228] In fact, clinical research can be valuable for individuals in the palliative care setting because they may seek to participate for their own potential benefit and to create meaning and value through contribution towards the greater good.[227] There is a need to ensure that policies are in place to respect potential participants' wishes and facilitate decision-making around research participation, rather than assuming their unwillingness to participate and depriving them of these opportunities.[65, 228] A safe and supportive environment for these individuals in clinical trials needs to be fostered, with barriers explored and overcome.

6.3 Limitations

This review had several limitations. Firstly, the study had stringent inclusion criteria concerning the required life expectancy (median survival of ≤ 4 weeks)

and the need to include clinically significant depressive symptom diagnoses using a validated method during the study randomisation process. However, given this extremely short prognosis sub-group's distinct care needs (e.g., little time for intervention effects, and the risk of intolerance), these stringent eligibility criteria were deemed necessary to generate meaningful and scientifically robust evidence.[10, 91] Secondly, this review excluded non-RCT studies. Due to the high number of RCTs exploring the effectiveness of depression interventions in various advanced life-limiting illness settings, this review included only RCTs to generate the highest level of evidence. Nonetheless, with no extractable data from RCTs for the target population, future systematic reviews could consider extending eligibility criteria to include non-RCT studies such as high-quality case-control studies. Thirdly, studies of non-malignant advanced life-limiting illnesses may have been under-represented, because those studies often did not measure functional status. Nonetheless, many studies of non-malignant diseases included survival data that were out of the range of the extremely short prognoses group. Fourthly, this review excluded depression intervention studies performed in the context of dementia due to the contentious nature of diagnosing depressive disorders in this setting.[206, 208] Nevertheless, only one study was excluded for this reason. Lastly, despite the lateral search, it is possible that interventional studies that were not categorised as RCTs were missed.

7. CONCLUSION

Evidence from RCTs supporting any non-pharmacological or pharmacological interventions for clinically significant depressive symptoms in people with extremely short prognoses is currently lacking. Clinicians need to be aware of the lack of evidence about the effectiveness of any depression interventions in this patient group. There is an urgent need to develop inclusive and feasible interventional research in this area to guide clinical practice and optimise depression care for the dying.

CHAPTER 4: CURRENT AUSTRALASIAN PALLIATIVE PHYSICIANS' AND PSYCHIATRISTS' APPROACHES, PERCEIVED BARRIERS TO AND POTENTIAL IMPROVEMENT STRATEGIES FOR SCREENING, ASSESSING AND MANAGEMING DEPRESSION IN PALLIATIVE PATIENTS WITH EXTREMELY SHORT PROGNOSES

1. PREFACE

The previous thesis chapters contain systematic reviews of the international literature that highlighted the high prevalence of clinically significant depressive symptoms and the lack of effective interventions in people with extremely short prognoses. Meanwhile, little is known about how these symptoms are screened, assessed, and managed by palliative physicians and psychiatrists in the palliative care population, and even more so when life expectancy is estimated to be in the range of days to weeks.

The knowledge of current Australasia palliative care physicians' and psychiatrists' practices in screening for, assessing and managing depressive symptoms in individuals with extremely short prognoses is pivotal for the development of a well-integrated depression care system in the palliative care setting. It may open the way to a more systematic approach to caring for depressive symptoms in palliative care patients with extremely short prognoses, facilitating closure at the end of life for these people and their loved ones.

This chapter presents a mixed-methods study using a sequential explanatory design (initial survey with qualitative components followed by a qualitative focus group study) exploring current Australasian palliative care physicians' and psychiatrists' practices in screening for, assessing and managing depressive symptoms in individuals with extremely short prognoses, and their perceptions of the key barriers to care and improvement strategies. It contains edited versions of the following published manuscripts (Appendices 6 & 7), presenting the quantitative and qualitative study components in an integrated manner to provide a deeper understanding of the issues of interest.

Lee, W., Chang, S., DiGiacomo, M., Draper, B., Agar, M. R., & Currow, D. C. (2022). Caring for depression in the dying is complex and challenging - survey

of palliative physicians. *BMC Palliative Care, 21*(1), 11. doi:10.1186/s12904-022-00901-y (Citations: 6; Altmetric: 5)

Lee, W., DiGiacomo, M., Draper, B., Agar, M. R., & Currow, D. C. (2022). A Focus Group Study of Palliative Physician and Consultation-Liaison Psychiatrist Perceptions of Dealing with Depression in the Dying. *Journal of Palliative Care, 37*(535-544). doi:10.1177/0825859722112145 (Citations: 0; Altmetric: 3)

2. BACKGROUND

Previous quantitative and qualitative studies in the UK and Australia suggested that palliative care clinicians displayed some uncertainty when dealing with depression in the palliative care population.[67, 69, 280] A survey of 175 Australasian palliative care physicians found that nearly half of the cohort (43%) assessed depression only sometimes, with the most frequently used screening method by being ultra-short screening tools, and that clinicians were unaware that these actually were screening tools.[67] Another survey of palliative care physicians' practice in the UK (n = 226) showed similar findings, with only 10% of the cohort using a validated questionnaire to screen for depression.[68] In terms of treatments for depression, a retrospective case note analysis of more than a thousand terminally ill patients in palliative care units in England found that more than 70% of palliative patients with depression did not receive potentially effective therapy, and those who received antidepressants were nearly always under-dosed.[149] However, these studies were not specifically designed to characterise palliative care clinicians' practices in the sub-group of people with extremely short prognoses. Appropriate strategies of depression assessment and management for these people might differ from those for other palliative care patients with longer prognoses. In fact, these studies suggested that clinicians had a sense of nihilism and were less likely to assess or treat depression in such cases.[67, 69, 280]

While palliative physicians and psychiatrists are integral to providing specialist depression care in the palliative care context,[281] no study to date has explored their perceptions of and approaches to depression care in people with

extremely short prognoses. There is also a lack of data from Australasia to inform local health service improvement.

Better knowledge of current Australasian palliative care physicians' and psychiatrists' practices in screening, assessing and managing depression for individuals with extremely short prognoses, as well as the perceived barriers and postulated improvement strategies, could be used to develop a well-integrated depression care system. It may open the way to a more systematic approach of caring for people with depression and advanced life-limiting illnesses with extremely short prognoses and their loved ones, facilitating closure in the end-of-life setting.

3. AIM

This mixed-methods study aimed to ascertain Australasian palliative care physicians' and psychiatrists' approaches to depression screening, assessment and management in the extremely short prognosis setting (estimated life expectancy of days to weeks), exploring key barriers to care and potential solutions.

4. RESEARCH DESIGN AND METHODOLOGY

4.1 Research Design

This research consisted of a cohort study with a sequential explanatory design, was informed by the theoretical framework of pragmatism, and used a mixed-methods approach (a quantitative survey with qualitative components followed by qualitative focus groups).[282-285]

4.2 Populations of Interest

- Palliative physicians: Australasian palliative physicians registered as current members of the Australian and New Zealand Society of Palliative Medicine (ANZSPM). This is the largest professional body of palliative medicine physicians in Australia and New Zealand, consisting of general practitioners and specialist physicians (e.g., palliative physicians, renal physicians, and radiation oncologists) with advanced training in palliative medicine

- Psychiatrists: Fellows and trainees of the Royal Australian and New Zealand College of Psychiatrists (RANZCP)

4.3 Methods of Data Collection

4.3.1 Survey

The anonymous online survey (Appendix 8) used the Research Electronic Data Capture (REDCap) platform. It contained branching logic with a maximum of 23 questions (four multiple-response questions and 19 single-response questions) for each respondent, tailored according to the respondent's self-identified primary discipline (palliative medicine or psychiatry) and previous encounters with patients with extremely short prognoses. It explored the domains of depression screening, assessment, management and integration between psychiatry and palliative care services for patients with extremely short prognoses based on extrapolation from the general palliative care literature and investigators' clinical experiences.[10, 67, 76, 112] In particular, clinicians' use of interventions that might produce rapid antidepressant effects in the extremely short prognosis setting, such as adjunct antipsychotics, psychostimulants, ketamine, and ECT, were explored.[107, 230, 286, 287] The survey contained two opened-ended questions asking about perceived challenges or barriers to effective assessment and management of depression in patients with extremely short prognoses. To increase feasibility, validity and reliability, the survey questions were developed by an investigator panel consisting of clinical academic experts in palliative care and psychiatry. The survey was piloted with four palliative physicians, and the results suggested no need to modify the questionnaire (which took, on average, eight minutes to complete).

4.3.2 Survey Recruitment

The survey link was distributed by the professional bodies to members on the 25th of February 2020 (ANZSPM) and the 1st of May 2020 (RANZCP). Due to the restrictions of the organisations' survey dissemination policies, capacity for sending reminder emails was limited: for ANZSPM, only one reminder email was sent after two weeks; for RANZCP, no reminder email could be sent to the

entire cohort, but one reminder email was sent to members of the College Faculty of Consultation Liaison, after six weeks (12th of June 2020). Apart from the RANZCP mass cohort distribution, in which the survey link was distributed as part of an electronic newsletter (*Psyche*), survey links were contained within the email distributed by the professional bodies (ANZSPM and RANZCP College Faculty of Consultation Liaison). The survey was closed on the 31st of July 2020. No financial incentives were offered to respondents.

4.3.3 Survey Sample Size Consideration and Data Analysis

The whole populations of RANZCP and ANZSPM, with 6655 and 522 fellows/trainees and members respectively, were invited to be surveyed. A conservatively expected online survey response rate of 20% for both ANZSPM and RANZCP cohorts was estimated based on articles detailing online survey methods in these cohorts in recent years[288-292].

Quantitative data were expressed as the number of respondents (percentage) and analysed using IBM SPSS Statistics 26.[293] Responses to the two open-ended items were analysed independently by two investigators (WL and MD) using conventional qualitative content analysis.[294, 295] WL is a palliative care physician with clinical experience as a psychiatry resident, and MD is an experienced qualitative health researcher. Codes were developed inductively through careful reading of the data and sorted into categories of related material in NVivo 12. Categories were refined, defined, and subcategories developed through analyst discussion until consensus was achieved.[294, 295] Quantification of responses within subcategories was performed using NVivo 12.[296]

4.3.4 Subsequent Focus Groups

Eligible participants were palliative physicians and psychiatrists based in Australasia who were members of ANZSPM (consisting of general practitioners and specialist physicians with advanced training in palliative medicine) and RANZCP. Participants were recruited through emailed invitations distributed by both organisations. Initially, only those who had completed the initial survey (n = 9; 60.0%) were eligible.[297] Due to poor recruitment, the invitation was extended

to include clinicians who were unsure about whether they had completed the survey (n = 4; 26.7%) or denied survey completion (n = 2; 13.3%) by two subsequent email invitations using purposive and snowball sampling. The organisations' dissemination policies restricted further email invitations.

4.3.5 Focus Group Data Collection

Three focus groups (two with palliative care physicians, one with consultation liaison [CL] psychiatrists) were conducted in November and December 2020. Each focus group contained four to eight participants to maximise dynamic group interaction and discussion, ensuring homogeneity and reducing inhibition about expressing viewpoints.[298, 299] It was expected that using an inductive coding approach, 2-3 focus groups would capture at least 80% of the themes.[300]

The focus groups lasted for one hour each and were conducted online using Zoom. Only participants and facilitators were present in the discussions, and each participant attended the focus group once.

Two facilitators (authors) conducted the focus group discussions. The primary facilitator (WL) was a male palliative care specialist and research fellow undertaking clinical care and doctoral studies on this topic. The secondary facilitator (MD) was a PhD-qualified female academic with a background in psychology and experience in qualitative research with people with chronic and life-limiting illnesses. The primary facilitator was known to some palliative care participants as a clinical colleague, but not in a hierarchical relationship. The secondary facilitator was not known to any participants. While the primary facilitator facilitated the group discussion, the secondary facilitator moderated the discussion and recorded relevant field notes to aid data analysis. Importantly, the secondary facilitator observed the group dynamic closely to inform the primary facilitator about any participant who might have felt inhibited from expressing their viewpoint, and picked up important cues and topics that required further discussion.

Participants were emailed the initial survey results (Appendix 9) and were informed that they would be asked to comment on these during the focus

groups.[297] To begin each session, participants were asked about their general impression of depression in people with extremely short prognoses. The survey results were then presented by the primary facilitator.[297] Following this, participants were prompted to comment on the survey findings, elaborate on the perceived reasons for clinical practices and challenges, and postulate potential improvement strategies using open-ended questions designed *a priori* (Appendix 10).

4.3.6 Focus Group Data Analysis and Reporting

The focus group discussions were video-recorded with the participants' permission. The audio recordings were transcribed using a professional transcription service. The primary facilitator checked transcripts for accuracy, then the primary and secondary facilitators undertook conventional qualitative content analysis.[294, 295] They independently read and re-read transcripts, coded text inductively, and created coding trees using NVivo 12. They met to resolve differences and consolidate codes into agreed categories through multiple discussions between themselves and the rest of the authorship team (consisting of researchers and clinicians with backgrounds in palliative medicine or psychiatry) until 100% consensus was reached.

Data are reported according to general perceptions, challenges, and solutions. Following inductive analysis, categories of challenges and solutions were broadly influenced by McLeroy's ecological framework (applied post hoc) to organise data for reporting, because they reflect various levels of influence required to drive changes.[301] This qualitative study manuscript was written using the Consolidated Criteria for Reporting Qualitative Research framework.[302]

4.3.7 Data Management / Storage

The survey data, contact details for participants who agreed to participate in a focus group, and audio files/transcriptions were stored securely in the online Research Electronic Data Capture (REDCap) database (Vanderbilt University, Tennessee, United States, version 9.8.2, 2020). REDCap is a secure web-based software system for managing data in research and is protected via

Secure Sockets Layer encryption. Only the investigators have access to the REDCap database. Records from this study will be maintained for five years after publication.[303] Once the five-year waiting period is completed, the files will be erased from the hard drive.

4.3.8 Ethical Considerations

This project was approved by the UTS Human Research Ethics Committee (approval number: ETH19-4071). There were several ethical considerations in the running of this study. Firstly, there was a potential risk of the study inducing psychological distress for the participants through them recalling the challenging cases of depression that they had to assess and manage. The likelihood of this, and the severity of distress if it were to occur, were thought to be very low due to the culture of medical professionals seeking peer review and support when they encounter difficult cases. Meanwhile, the focus group setup could mitigate this risk further by providing participants with peer support. Nonetheless, participants were informed of this risk and were encouraged to seek collegial or other professional support if significant distress occurred, including support from general practitioners, psychotherapists, or psychiatrists.

Another consideration relates to potential pre-existing relationships between researchers and participants. Given most of the researchers were clinicians in the fields of palliative care and psychiatry in Australasia, there was the possibility that the researchers would encounter participants (fellow doctors) with whom they were acquainted as friends or with whom they had collegial relationships. The anonymous nature of the survey minimised any risk of undue pressure on participants to participate due to pre-existing relationships with the researchers. The researchers did not ask potential participants (colleagues and clinician friends) to participate in this study personally, only via the general invitation sent by the professional society/body electronically. As outlined on the questionnaire's cover page and the participant information sheet for the qualitative study, participation was completely voluntary.

Lastly, steps were taken to protect the confidentiality and privacy of the participants, including the anonymous nature of the survey, storing recordings of

the online focus groups securely in REDCap where only investigators could access them, and de-identifying participants in the recording transcripts and published data.

5. RESULTS

5.1 Part A: Survey Results

Completed surveys were obtained from 110 individuals: 79 responses from 522 members of ANZSPM (15.1%); and 31 of 6655 RANZCP members (0.5%). Of the 110 responses, 72 respondents identified their primary specialty as palliative medicine, and 32 as psychiatry (Table 4.1). Only results from those who identified themselves primarily as palliative physicians and psychiatrists (n = 104) are reported. Participating clinicians were mainly specialists and fellows (79.8%); aged 31-60 years (83.7%); primarily working in Australia (82.7%); had graduated more than 10 years ago (90.3%); and were working ≥ 20 clinical hours per week (87.5%). Most clinicians (n=97; 93.3%) reported having encountered depression in people with extremely short prognoses. There were no statistically significant demographic differences between the palliative physicians (n = 70; 97.2%) and psychiatrists (n = 27; 84.4%) (p = 0.05).

TABLE 4. 1. DEMOGRAPHICS OF RESPONDENTS

	Palliative Physicians (n = 72)	Psychiatrist (n = 32)	Total (n = 104)	p value‡ (<0.05*)
Position				0.070
Specialist & Fellow	53 (73.6%)	30 (93.8%)	83 (79.8%)	
Trainee	16 (22.2%)	2 (6.3%)	18 (17.3%)	
Other	3 (4.2%)	0 (0.0%)	3 (2.9%)	
Another training background	42 (58.3%)	7 (22.6%)	49 (47.6%)	0.001*
Gender				0.163
Male	18 (25%)	13 (40.6%)	31 (29.8%)	
Female	54 (75.0%)	19 (59.4%)	73 (70.2%)	
Country				0.011*
Australia	55 (76.4%)	31 (96.9%)	86 (82.7%)	
New Zealand	17 (23.6%)	1 (3.1%)	18 (17.3%)	
Years Since Medical Graduation				0.669
<10 years	8 (11.1%)	2 (6.3%)	10 (9.6%)	
10–19 years	27 (37.5%)	11 (34.4%)	38 (36.5%)	
20 or more years	37 (51.4%)	19 (59.4%)	56 (53.8%)	
Age				0.169
21–30	2 (2.8%)	1 (3.1%)	3 (2.9%)	
31–40	20 (34.7%)	6 (18.8%)	31 (29.8%)	
41–50	15 (20.8%)	9 (28.1%)	24 (23.1%)	
51–60	23 (31.9%)	9 (28.1%)	32 (30.8%)	
61–70	7 (9.7%)	5 (15.6%)	12 (11.5%)	
71–80	0 (0.0%)	2 (6.3%)	2 (1.9%)	
Clinical Hours/ week				0.344
< 10	2 (2.8%)	2 (6.3%)	4 (3.8%)	
10–19	5 (6.9%)	4 (12.5%)	9 (8.7%)	
20–29	15 (20.8%)	10 (31.3%)	25 (24.0%)	
30–39	32 (44.4%)	9 (28.1%)	41 (39.4%)	
40 or more	18 (25.0%)	7 (21.9%)	25 (24.0%)	
Clinical Role				
Community (patient home, group home and residential aged care facilities):	35 (48.6%)	5 (15.6%)	40 (38.5%)	0.001*
Outpatient clinic	35 (48.6%)	23 (71.9%)	58 (55.8%)	0.022*

Consultative service in acute hospital	45 (62.5%)	25 (78.1%)	70 (67.3%)	0.088
Acute inpatient (palliative care or psychiatry wards in acute hospital)	28 (38.9%)	4 (12.5%)	32 (30.8%)	0.005*
Subacute hospital (palliative care unit / hospice / subacute psychiatry unit)	30 (41.7%)	3 (9.4%)	33 (31.7%)	0.001*
Encounter depression in extremely short prognoses	70 (97.2%)†	27 (84.4%)	97 (93.3%)	0.100

† This number included a palliative medicine respondent (n = 1) who answered "other" when asked about previous encounter of depression in the extremely short prognosis setting due to difficulty in distinguishing pathological depressed mood from normal grief.

‡ Fisher's Exact Test, 2-sided

Most clinicians (n = 64; 61.5%) reported that they screen for depression in general palliative care patients, while only 42.3% (n= 41 out of 97) encountering patients with extremely short prognoses reported screening for depression. There was no significant difference between the palliative medicine and the psychiatry cohorts (68.6% vs 59.3%, p = 0.29).

Among clinicians who might screen for depression (answered "yes" or "depends") in general palliative care patients, the primary screening method reported was a clinical interview (n = 74; 92.5%), followed by asking the family/carers (n = 54; 67.5%), asking other health professionals involved in the care (n = 51; 63.8%), and the use of screening tools (n = 32; 40.0%). For the extremely short prognoses group, while 71.1% (n = 69) of clinicians reported no difference in the way of screening compared to the general palliative population, 16.5% (n = 16) reported a "difference": taking a more reactive rather than proactive approach; being briefer in assessment; relying more on objective information sources; and putting less emphasis on somatic symptoms. More palliative physicians than psychiatrists used screening tools (27 of 57 [47.4%] versus 5 of 23 [21.7%], p = 0.04). There were significant differences in the types of tools used: while palliative physicians tended to use the ultra-short questionnaire (one or two item questionnaires: n = 5, 8.8%; n = 14; 24.6% respectively), psychiatrists only used more detailed tools (e.g., HADS [n = 2;

8.7%]) (p = 0.001). Only one palliative physician respondent reported using the HADS.

For depression assessment, at least 80% of clinicians said they would ascertain whether the depression episode was first or recurrent during the assessment, regardless of whether the prognosis was extremely short. All clinicians who had encountered depressed patients with extremely short prognoses experienced uncertainty regarding the cause of depression. Most clinicians (palliative physicians: n = 56, 80.0%; psychiatrists: n = 25, 92.6%) reported that they would treat the depressed mood despite the uncertain cause. The primary sources of assistance sought by palliative physicians in this context were psychiatry (n = 33; 47.1%) and psychology (n = 29; 41.4%) professionals. Meanwhile, 25.9% (n = 7) of psychiatrists said they would seek psychology input in this context.

For depression somatic symptom assessment, the majority (n = 49; 47.1%) of clinicians reported including somatic symptoms in the general palliative care patients while excluding somatic symptoms in the sub-group with extremely short prognoses (n = 35; 36.1%). Notably, in the setting of extremely short prognoses, 35.1% (n = 34) of clinicians reported “depends”: whether the somatic symptoms could be attributable to the nature of the terminal illnesses and associated interventions on an individual basis; and that somatic symptoms were still valuable to be considered in the “overall picture” of the patient.

For various treatment approaches for major depressive disorder in extremely short prognoses, most clinicians reported using non-pharmacological approaches (n = 86; 88.7%), followed by the use of typical antidepressants (n = 85; 87.6%). When comparing the likelihood of using various depression interventions in the extremely short prognoses sub-group as compared to the general palliative care cohort, the majority of clinicians reported: no difference in using non-pharmacological interventions (n = 37; 38.1%); being less likely to use typical antidepressants (n = 43; 44.3%); more likely to use benzodiazepines (n = 35; 36.1%); and not using psychostimulants (n = 29, 29.9%), atypical antipsychotics (n = 28, 28.9%), novel treatment/experiment trials (n = 61; 62.9%), or ECT (n = 54; 55.7%). There were bimodal distributions with the

highest prevalence values of “I don’t use” and “more likely to use” for treatment options of: psychostimulants (n = 29; 29.9% - “I don’t use” and n = 24; 24.7% - “more likely”); atypical antipsychotics (n = 28; 28.9% - “I don’t use” and n = 27; 27.8% - “more likely”); benzodiazepines (n = 29; 29.9% - “I don’t use” and n = 35; 36.1% - “more likely”); and novel medication/experimental trials (n = 61; 62.9% - “I don’t use” and n = 12; 12.4% - “more likely”). Due to technical issues in the online survey platform, the psychostimulant item was initially not available for the first 28 ANZSPM participants, leading to the large proportion of non-response (n = 27; 38.6%) for this item.

There were significant differences between palliative physicians and psychiatrists in the likelihood of using various depression interventions to treat depressed patients with extremely short prognoses (Table 4.2). Notably, fewer palliative physicians than psychiatrists reported being “more likely” to use non-pharmacological interventions (17.1% vs 37.0%, p = 0.001), while palliative physicians reported more “I don’t use” for non-typical antidepressant pharmacological interventions (e.g., atypical antipsychotics, benzodiazepines, novel treatments).

TABLE 4. 2. CLINICIANS' APPROACHES TO MAJOR DEPRESSIVE DISORDER IN PALLIATIVE PATIENTS WITH EXTREMELY SHORT PROGNOSES VERSUS BETTER PROGNOSES

INTERVENTION	RESPONSE	SPECIALTY			*P value*
		Palliative medicine (n = 70) [counts (%)]	*Psychiatry (n = 27) [counts (%)]*	*Total[v] (n = 97) [counts (%)]*	
a. Non-pharmacological interventions (e.g., supportive psychotherapy / counselling, cognitive therapy)	I don't use	2 (2.9)	0 (0)	2 (2.1)	0.001*
	Less likely (cumulative)	26 (37.1)	1 (3.7)	27 (27.8)	
	No difference	26 (37.1)	11 (40.7)	37 (38.1)	
	More likely (cumulative)	12 (17.1)	10 (37.0)	22 (22.7)	
	No response	4 (5.7)	5 (18.5)	9 (9.3)	
b. Typical antidepressant	I don't use	3 (4.3)	0 (0)	3 (3.1)	0.026*
	Less likely (cumulative)	36 (51.4)	7 (25.9)	43 (44.3)	
	No difference	18 (25.7)	13 (48.1)	31 (32)	
	More likely (cumulative)	9 (12.9)	2 (7.4)	11 (11.3)	
	No response	4 (5.7)	5 (18.5)	9 (9.3)	
c. Psychostimulant (e.g., methylphenidate, modafinil)[≠]	I don't use	18 (25.7)	11 (40.7)	29 (29.9)	0.17
	Less likely (cumulative)	3 (4.3)	1 (3.7)	4 (4.1)	
	No difference	4 (5.7)	4 (14.8)	8 (8.2)	
	More likely (cumulative)	18 (25.7)	6 (22.2)	24 (24.7)	
	No response	27 (38.6)	5 (18.5)	32 (33)	
d. Atypical antipsychotics (e.g., risperidone, olanzapine)	I don't use	26 (37.1)	2 (7.4)	28 (28.9)	0.010*
	Less likely (cumulative)	6 (8.6)	3 (11.1)	9 (9.3)	
	No difference	14 (20)	10 (37)	24 (24.7)	
	More likely (cumulative)	20 (28.6)	7 (25.9)	27 (27.8)	
	No response	4 (5.7)	5 (18.5)	9 (9.3)	

e. Benzodiazepine	I don't use	28 (40.0)	1 (3.7)	29 (29.9)	0.001*
	Less likely (cumulative)	2 (2.9)	2 (7.4)	4 (4.1)	
	No difference	12 (17.1)	8 (29.6)	20 (20.6)	
	More likely (cumulative)	24 (34.3)	11 (40.7)	35 (36.1)	
	No response	4 (5.7)	5 (18.5)	9 (9.3)	
f. Novel medication / experimental trials (e.g., ketamine, esketamine nasal spray)	I don't use	49 (70)	12 (44.4)	61 (62.9)	<0.001*
	Less likely (cumulative	4 (5.7)	3 (11.1)	7 (7.2)	
	No difference	1 (1.4)	7 (25.9)	8 (8.2)	
	More likely (cumulative)	12 (17.1)	0 (0)	12 (12.4)	
	No response	4 (5.7)	5 (18.5)	9 (9.3)	
g. Electroconvulsive therapy	I don't use	51 (72.9)	3 (11.1)	54 (55.7)	<0.001*
	Less likely (cumulative)	10 (14.3)	15 (55.6)	25 (25.8)	
	No difference	4 (5.7)	4 (14.8)	8 (8.2)	
	More likely (cumulative)	1 (1.4)	0 (0)	1 (1)	
	No response	4 (5.7)	5 (18.5)	9 (9.3)	

*indicates statistically significant differences ($p < 0.05$) between palliative medicine and psychiatry cohorts using Fisher's Exact Test (2-sided).

≠ Due to a technical fault, the survey item exploring psychostimulant use was initially not accessible to the first 28 ANZSPM respondents.

For interdisciplinary collaboration, at least 40% of clinicians reported requesting and being asked for advice by the other specialty on a cumulatively monthly or more frequent basis (Table 4.3). The majority of participants from both disciplines (palliative physicians: n = 48; 66.7%; psychiatrists: n = 12; 37.5%) thought contact frequency with the other specialty should be increased.

TABLE 4. 3. PALLIATIVE CARE AND PSYCHIATRY SERVICE LINKAGE

Palliative Medicine (n = 72)		***Number (%)***
For assessment and management of depression in the overall palliative care setting, on average how often have you asked psychiatry for input?	Never	3 (4.2)
	Yearly or longer	16 (22.2)
	Monthly or longer	41 (56.9)
	Weekly or longer	6 (8.3)
	Daily or longer	0 (0.0)
	No response	6 (8.3)
For patients with depression and palliative care needs, on average how often have you been asked by psychiatry to provide palliative care management advice?	Never	24 (33.3)
	Yearly or longer	26 (36.1)
	Monthly or longer	15 (20.8)
	Weekly or longer	1 (1.4)
	Daily or longer	0 (0.0)
	No response	6 (8.3)
For optimal patient care, do you think contact frequency with psychiatry should be:	More frequent	48 (66.7)
	About right	9 (12.5)
	Other	9 (12.5)
	No response	6 (8.3)
Psychiatry (n = 32)		***Number (%)***
For patients with depression and palliative care needs, on average how often have you ask palliative care for management input?	Never	2 (6.3)
	Yearly or longer	3 (9.4)
	Monthly or longer	9 (28.1)
	Weekly or longer	5 (15.6)
	Daily or longer	2 (6.3)
	No response	11 (34.4)
For assessment and management of depression in the overall palliative care setting, on average how often would you get asked by palliative care for input?	Never	0 (0.0)
	Yearly or longer	7 (21.9)
	Monthly or longer	7 (21.9)
	Weekly or longer	7 (21.9)
	Daily or longer	0 (0.0)
	No response	11 (34.4)
For optimal patient care, do you think contact frequency with palliative care should be:	More frequent	12 (37.5)
	Less frequent	1 (3.1)
	About right	8 (25.0)

	No response	11 (34.4)

Ninety-one respondents (87.5%) answered the open-ended questions regarding key challenges or barriers to effective assessment and management of depression in palliative care patients with extremely short prognoses. Respondents commented on the complexity of the clinical situation with interactions between physical, psychosocial, and spiritual dimensions. Reported key challenges and barriers are listed in Table 4.4, categorised under the domains of patient, clinician, health system, literature, and society. The three most frequently reported barriers were perceived frailty, burden and intolerance of depression assessment and management on the patient (64.8%); the lack of therapeutic options that are rapidly effective (60.4%); and the complexity in differentiating the symptoms of terminal illness from the somatic symptoms of depression (41.8%).

Table 4. 4. Reported Challenges/Barriers to Depression Assessment and Management in People with Extremely Short Prognosis

DOMAINS/SUBCATEGORIES	PREVALENCE OF REPORTING OF SUBCATEGORIES AMONG RESPONDENTS (N = 104) (%)	EXAMPLE QUOTES
Patient - frailty, co-existing symptom burden and competing priorities of associated end-of-life issues when time for intervention effects is poor		
• Frailty, Burden & Intolerance*	64.8%	• "Fatigue, nausea, pain" (Participant 72) and "declining cognition" (Participant 27) • "Even when good psychology, psychiatry and/or pastoral care are available these patients are often too fatigued to participate in talking therapies" (Participant 25) • "Lack of effective medication which will make a difference without causing unnecessary side effects" (Participant 6)
• Therapeutic Efficacy - Lack of therapeutic options that are rapidly effective in the context of extremely short prognoses*	60.4%	• "Time frame required for effect of pharmacologic and non pharmacologic interventions" (Participant 5) • "Timing and the poor prognosis which impedes any intervention to be effective." (Participant 2)
• Competing priorities - Prioritisation of physical or other psychosocial & spiritual co-existing issues, symptoms, or goals	19.8%	• "Competing priorities - physical symptoms and planning for end-of-life are often more pressing" (Participant 25) • "Other symptoms take priority and are focused on much more than mood disorders" (Participant 44)
Clinician - self-perceived limitations in psychiatry skills in the palliative care setting with incompetence in diagnostic differentiation		
• Challenging diagnostic differentiation		

○ Depression vs terminal illness symptoms*	41.8%	• "Challenges differentiating somatic symptoms from depression vs physical illness" (Participant 5) • "Usually hard to tease out how much is depression and how much is part of dying process" (Participant 13)
○ Between depressed-mood syndromes or differentials (e.g., existential distress, demoralisation, adjustment disorder, organic brain syndrome)	17.6%	• "Challenges differentiating demoralisation from major depression" (Participant 5) • "Distinguishing between adjustment and depression" (Participant 8) • "Misattribution – e.g., depression with psychotic symptoms being attributed to delirium" (Participant 4)
○ Normal vs Pathological	13.2%	• "Hard to distinguish from normal grief" (Participant 19) • "Difficulty assessing the difference between normal reactive mood changes [versus] pathological level of mood changes" (Participant 68)
• Limited Skills & Training	22.0%	• "Limited skills in psychiatric assessment - my last psychiatry placement was as a 3rd year medical student" (Participant 60) • "Limited knowledge of what works to improve mood in limited time frame" (Participant 41) • Very few psychiatrists are comfortable working in the clinical space [palliative care]" (Participant 90)
System – Inadequate health system resources and access to required interventions in the local health services		

• Suboptimal access and delivery of palliative care and mental health services	29.7%	• “High patient numbers for a small number of clinicians; Lack of allied health staff in [palliative care] MDT to deliver interventions” (Participant 31) • “Poor access to psychology/psychiatric services” (Participant 44) “ • Lack of allied health staff in [palliative care] MDT to deliver interventions” (Participant 37)
• Lack of access to desired depression interventions	12.1%	• “Lack of access to resources for non-pharmacological management e.g., psychology, music therapy” (Participant 71) • “Access to rapid-acting medications like modafinil” (Participant 42)
• Suboptimal external environment	3.3%	• “Lack of private interview space in acute ward” (Participant 89) • “[Lack of] control of clinical environment” (Participant 31)
• Language & cultural issues	2.2%	• “Language / cultural barriers” (Participant 64) • “Access to interpreters” (Participant 103)
Literature - Heterogeneity of depression concept and the lack of evidence to guide practice in the extremely short prognosis setting		
• Lack of evidence & guidelines	11.0%	• “Uncertainty regarding the best treatment for this population/limited evidence base” (Participant 56)
• Heterogeneity of the concept and definition of depression in an extremely short prognosis setting	2.2%	• “Lack of defined criteria for diagnosis of depression in this group of patients” (Participant 48)
Society – Unsupportive attitudes and beliefs of patients, family and clinicians that prevents optimisation of depression care		
• Nihilism / Futility	11%	• "A sense of futility - Why assess it if there's little I can do about it?“ (Participant 25)

		• "Therapeutic nihilism" (Participant 21)
• Acceptance / Normalisation	9.9%	• "Acceptance that this [depression] is a normal part of end of life" (Participant 21) • "Normalisation" (Participant 40) • "Of course he/she is depressed, he/she is dying" (Participant 4)
• Resistance / Disinclination of patients, the public, family, or clinicians/staff	7.7%	• "Stigma" (Participant 65) • "Pressure from other health care professionals not to treat patients as they are dying" (Participant 34) • "Family not willing to engage non-pharm [interventions]" (Participant 64)

*Top three most commonly reported barriers: the perceived frailty, burden and intolerance of depression assessment and management on the patient (64.8%); the lack of therapeutic options that are rapidly effective (60.4%); and the complexity in differentiating the symptoms of terminal illness from the somatic symptoms of depression (41.8%).

5.2 Part B: Focus Group Results

Overall, 15 clinicians participated (Table 4.5) - 11 palliative physicians and four CL psychiatrists, predominantly (> 90%) based in Australia, with mean years of specialty experience of 10.7 (SD: 6.4) and 15.5 (SD: 5.1) respectively.

TABLE 4. 5. FOCUS GROUP PARTICIPANT CHARACTERISTICS

	Palliative Medicine (n = 11)		Psychiatry (n = 4)	
	Details	**n (%)**	**Details**	**n (%)**
Background / Subspecialties	General Practitioner	3 (27.3%)	Consultation Liaison	4 (100%)
	Specialist Physician	8 (72.7%)		
Position	Specialist	10 (90.9%)	Specialist	4 (100%)
	Trainee	1 (9.1%)	Trainee	0 (0%)
Had experiences with palliative care patients	Yes	11 (100%)	Yes	4 (100%)
Country	Australia	10 (90.9%)	Australia	4 (100%)
	New Zealand	1 (9.1%)	New Zealand	0 (0%)
Regionality of Work*	Urban	10 (90.9%)	Urban	4 (100%)
	Regional/Rural	1 (9.1%)	Regional/Rural	1 (25%)
Setting of Services*	Community (Home/Residential aged care)	9 (81.8%)	Community (Home/Residential aged care)	0 (0%)
	Outpatient Clinic	5 (45.5%)	Outpatient Clinic	2 (50.0%)
	Inpatient Palliative Care Unit /Hospice	6 (54.5%)	Inpatient Mental Health Unit	1 (25.0%)
	Consult	6 (54.5%)	Consult	3 (75.0%)
Public /Private*	Public	11 (100%)	Public	3 (75.0%)
	Private	3 (27.3%)	Private	3 (75.0%)
Previous Survey Completion	Yes	5 (45.5%)	Yes	4 (100%)
	Unsure	4 (36.4%)	Unsure	0 (0%)
	No	2 (18.2%)	No	0 (100%)

*Multiple-response item (compared to other single-response items).

5.2.1 General Perceptions

When asked about their overall perceptions, the participants described the topic of depression care in people with extremely short prognoses as *"complex"*. A sense of disempowerment was expressed among the palliative physicians: *"uncertainty", "…it just makes me a bit depressed",* and *"[I feel] helpless"*.

> *"I think…there was the lack of skills [in depression screening, assessment, and management] and we don't really know... We can't do anything, so then we're less likely to want to assess it." (Palliative Physician 2)*

In contrast, while reflecting a sense of the topic's complexity, CL psychiatrists conveyed a sense of empowerment and optimism that depression in this context is still "*worth treating*" and "*not necessarily inevitable*".

> *"I think people are more treatable than a lot of people think. People think there's an inevitability of depression and an understandability about it, but that's not always the case." (Psychiatrist 3)*

Comparisons of perspectives of palliative physicians and psychiatrists revealed differences in the perceived roles and needs of the two specialities, with palliative physicians describing the need for guided first-line depression care delivery, and psychiatrists reporting inadequate resources to deliver second-line care (Table 4.6). Perceived key challenges and postulated potential solutions were described, synthesised *post hoc* into levels of influences informed by McLeroy's ecological framework (Table 4.7).[301]

TABLE 4. 6. COMPARISON OF PALLIATIVE MEDICINE AND PSYCHIATRY COHORTS IN FOCUS GROUPS

DOMAINS	PALLIATIVE MEDICINE (DIFFERENCES)	OVERLAP/SIMILARITIES	PSYCHIATRY* (DIFFERENCES)
General "one-word" impression for this topic	• Sense of Disempowerment	• Complexity of topic	• Sense of Empowerment
Perceived role	• Breadth-Focus (Coverage of all competing distresses (physical and psycho-existential) • Implementing initial screening, assessment and management for depression	• Perceived differences in roles for each discipline	• Depth-Focus (Covering specific psycho-existential distresses) • Detailed/focused assessment and management of specific mental health issues referred by palliative care
Screening & Assessment	• Require a more structured/guided approach (e.g., a framework or action plan)	• Methods need to be tailored to individual clinicians' skills	• Require flexibility/room for clinical judgement
Management	• Require more knowledge of non-pharmacological and pharmacological interventions	• Having issues with irrational prescribing of anti-depressants • Need to optimise non-pharmacological interventions	• Require more funding and resources to administer potentially effective interventions
Research	• Optimistic – perceiving potential solutions to improve research by modifying clinical trials designs	• Concerns of the potential harms outweigh the benefits for enrolling depressed patients with extremely short prognoses	• Pessimistic - ethical concerns of clinical trials in this population

		patients into clinical trials	
Service Integration/ Referral	• Palliative physicians' perception of undesirable outcomes from psychiatry assessment	• Agree with the need for *routine* contact/liaison between palliative medicine and psychiatry	• Psychiatry's perception of the lack of skills of palliative physicians in depression care processes

*The psychiatrists' viewpoints here were represented by four consultation liaison psychiatrists, with no representation from general psychiatrists.

TABLE 4. 7. PERCEIVED KEY BARRIERS AND CHALLENGES TO DEPRESSION CARE FOR PEOPLE WITH EXTREMELY SHORT PROGNOSES AND POSTULATED SOLUTIONS BY AUSTRALASIAN PALLIATIVE PHYSICIANS AND PSYCHIATRISTS

BARRIERS/CHALLENGES	POSTULATED SOLUTIONS
Provider Level	
• Palliative physicians and psychiatrists lacked training and uniformity in depression screening, assessment and management when caring for people with extremely short prognoses, and reported concerns of causing harm to patients and relationships through the care processes.	• Introduce psycho-existential distress screening to existing generic symptom screening tools utilised in palliative care services (e.g., Palliative Care Outcome Collaboration [PCOC] Symptom Assessment Scale [SAS]) to improve depression screening. • Develop consensus approach to care between palliative medicine and psychiatry that is tailored to individual clinician's skill-level. • Train clinicians with low-burden depression screening, assessment and management approaches via regular palliative care and psychiatry contacts (e.g., shared education), including the ability to differentiate, formulate and respond appropriately to depression when caring for people with extremely short prognoses.
Health Systems Level	
• The lack of access to required interventions and resources (e.g., clinical psychology) and suboptimal palliative care and	• While advocating for funding to better resource palliative care and psychiatry services, interim resources can be

psychiatry service linkage with associated negative clinician perceptions towards the other specialty adversely impact on patient care.	optimised by utilising community resources (e.g., volunteers and community initiatives) and strategies that improve existing palliative care and psychiatry service linkage (e.g., integrative multidisciplinary team meeting and ward round). • Develop a tiered referral model for psychiatry services tailored to individual palliative care services. • "Deformalise" the psychiatry referral thresholds so that palliative physicians do not perceive the referrals to require prior establishment of provisional psychiatric disorders but clinically significant symptoms.
Research Level	
• Supportive evidence for screening, assessment, and management of depression for people with extremely short prognoses is lacking with clinicians concerned about the feasibility, burden, and ethics of involving these people in experimental trials.	• Foster integrative research between palliative care and psychiatry, exploring various depression assessment and intervention methods and using innovative clinical trial designs to address feasibility and ethical concerns (e.g., Pre-consent/N-of-1).
Society/Culture Level	
• Stigma of mental health issues could have affected depression assessment and management at the end-of-life.	• Rebrand psychiatric services as part of routine palliative care service provision to enhance patient acceptance of psychiatric assessment and interventions.

5.2.2 Barriers & Challenges

Provider-Level

Overall, participants perceived that clinicians lacked the required training and intra- and inter-disciplinary uniformity in approaches to depression care in people with extremely short prognoses. Palliative physicians were perceived to lack the necessary psychiatric skills and have poor knowledge of therapeutic options while psychiatrists were perceived to lack the required palliative medicine training to deliver optimal depression care at the end of life.

> *"I think it's skills [identifying and responding to depression] that palliative care physicians should have, but the simple fact is they don't, some of them." (Psychiatrist 3)*

> *"[Psychiatrists] who aren't experienced in the area [palliative medicine], as soon as a patient expresses "I wish it was just all over," which is a pretty normal thing to say, they suddenly think they're suicidal..." (Palliative Physician 6)*

Clinicians reported concerns about causing harm to patients and relationships through depression care processes: depression screening using lengthy questionnaires might *"fracture"* the therapeutic relationship; interventions may cause adverse effects while not producing timely benefits; and peer pressure against administering potentially helpful interventions that have little supportive evidence. In separate focus groups, two participants voiced that depression can be perceived as a *"driver"* for people to make meaningful social interactions and treating it might cause harm.

> *"I wouldn't want to be robbing people of appropriate drivers to help people at the end-of-life (by treating their depression). The stress (depression) can be a driver to bring people together in a way if you do it right." (Palliative Physician 7)*

> *"Are we robbing people of appropriate sorrow by diagnosing them with depression and treating them?" (Palliative Physician 2)*

Health System-Level

Clinicians perceived a general lack of access to required liaison psychiatry and psychology services, especially those with palliative care expertise, even in urban settings where resources and skilled personnels tend to be more readily available.

> *"It goes back to resources. It just keeps going back to it. You [palliative physicians] can screen all you want, but if there's nobody [liaison psychiatry and psychology services with palliative care expertise] there to help you as a palliative care physician, you might do a good job of it, but you might feel under-supported..." (Psychiatrist 4)*

Access to potentially effective interventions was impacted by regulatory issues, contributed by the limited evidence-base in the literature.

> *"The other issue that comes up with novel treatments [in context of ketamine] or non-standard treatments are the limitations of the evidence-base and regulatory issues, which vary from state to state." (Palliative Physician 1)*

Participants noted that linkage and collaboration between existing palliative care and psychiatry services were often suboptimal. Negative clinician perceptions towards the other discipline were described to have contributed to the infrequent contact and late referrals. For example, some palliative physicians perceived undesirable assessment outcomes from psychiatry referrals.

> *"My CL service at one site, definitely, everybody seemed to have 'adjustment disorder'…But I think sometimes it gets a bit tiring to see 'adjustment disorder'...it just affects how often I want to ask them to come and give help really…" (Palliative Physician 8)*

Research-Level

A lack of evidence to support various assessment methods and interventions in people with extremely short prognoses was seen as a key challenge, because there was reluctance to enrol these individuals in clinical trials. While palliative

physicians reported concerns around the feasibility and burden of clinical trials for participants, CL psychiatrists voiced ethical concerns about patients possibly receiving ineffective interventions during randomisation.

> *"…there is a lot of barriers with researching in this patient group because we don't have a lot of time to get to them, and also the burdens often catch up and you have to weigh up…often research has a lot of questionnaires…that can be very challenging in such a difficult time" (Palliative Physician 11)*

> *"I did a small pilot trial looking at ICBT [Internet-based Cognitive Behavioural Therapy] in people with advanced cancer, but you can't randomise them, you know...[it's a] very ethically problematic thing to do. Like you can, but it would be really hard to go through the ethics board. And also personally I would find that hard!" (Psychiatrist 4)*

Society-Level

Stigma related to mental health issues was reported as a barrier to care. Participants opined that patients did not see discussions around psychological needs and having liaison psychiatry or psychology input as the norm, contributing to resistance to depression care.

> *"…a lot of patients, particularly in certain age groups where you never talked about psychiatric issues, and then when they're at the end of life and you start to bring that up, they get quite 'What do you mean?'" (Palliative Physician 2)*

5.2.3 Potential Solutions

Overall, the potential solutions postulated by participants involved an integrative approach established upon the foundation of better collaboration between both palliative care and psychiatry disciplines (Figure 4.1 & Table 4.7).

Provider-Level

Screening

For better depression recognition, participants postulated that low-burden depression screening as part of general screening for psycho-existential distress be added to the current generic symptom screening tool (e.g., Palliative Care Outcome Collaboration Symptom Assessment Scale [PCOC SAS]) used in palliative care services.

> *"..[Depression screening] being part of the PCOC scoring might be helpful, part of the standard scoring that we do before we see the patient...That might just help alert us there's something else that we need to screen for." (Palliative Physician 11)*

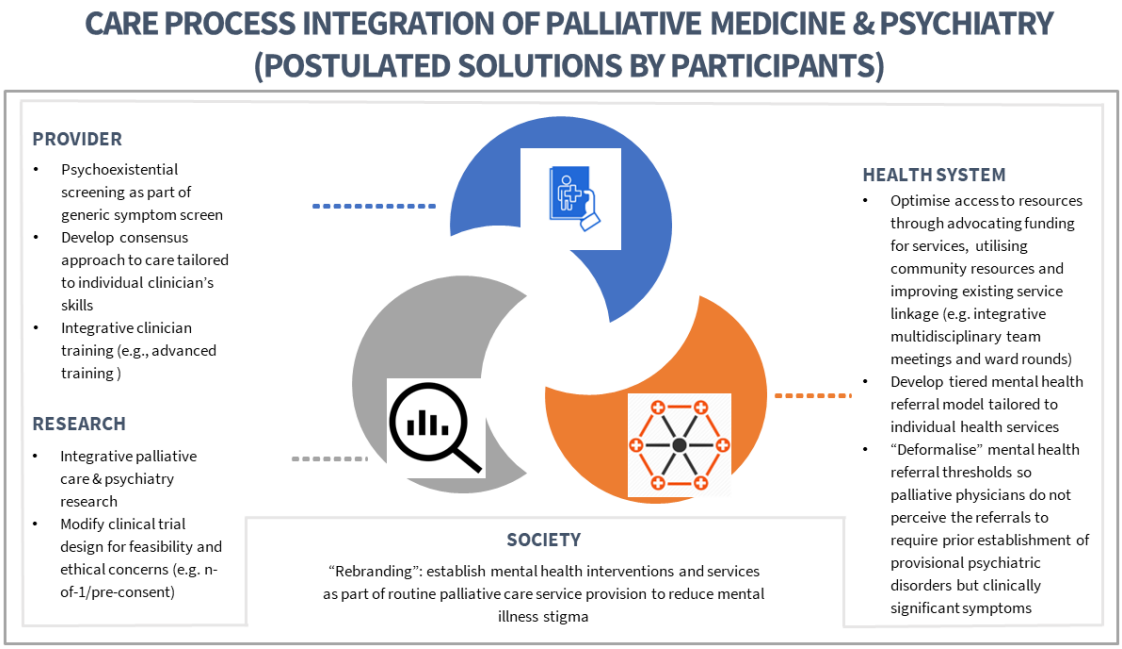


FIGURE 4. 1. CARE PROCESS INTEGRATION OF PALLIATIVE MEDICINE AND PSYCHIATRY – POSTULATED SOLUTIONS BY PARTICIPANTS.

Development of Consensus Approach

Participants perceived the need for palliative care and psychiatry to develop a consensus approach to care using the best available evidence. They argued that the approach needs to be tailored to the skill-level of individual clinicians - a structured approach to guide less experienced clinicians, and a flexible approach relying more on clinical judgment for the more experienced.

> *"I felt like maybe we, as two groups, need to get together and talk about what is actually the best way to manage these patients' depression - because I think there are two very different disciplines, and two very different skill sets that we need to marry to come up with a best way to approach this treatment." (Palliative Physician 11)*

Improve Clinician Training

Participants asserted that palliative physicians can be trained with low-burden approaches to depression care. They suggested the training content could include: the use of ultra-short screening methods such as one- or two-item

depression screening tools; the skills to differentiate and formulate the complex interplay of biopsychosocial aetiology during depression assessment;[304] and the ability to respond appropriately to depressed patients with the knowledge of potentially rapid-onset therapeutic options (i.e., methylphenidate and ketamine). In addition, they argued that psychiatrists need the foundational knowledge of general management of symptoms and end-of-life issues, and clinician training can occur through establishing regular interdisciplinary contacts, shared education, integrative advanced training, and formal education.

> *"…increasing exposure to junior medical staff [including palliative care trainees] to psychiatry rotations, so that there's capacity building and so that people have a basic building block of how to actually do psychiatrist assessments and start treatment...That [integrative training between palliative care and psychiatry] would be excellent." (Psychiatrist 3)*

Health System & Service-Level

Optimising Resources

While participants reported a need for more funding to better resource the palliative care and liaison psychiatry services, participants also postulated strategies to optimise interim resources. Community resources such as volunteers and community initiatives may be utilised to deliver necessary non-pharmacological interventions that do not necessitate psychiatry or psychology services. Strategies to improve the current linkage between existing psychiatry and palliative care services may optimise resource access. This can include establishing routine palliative care–CL psychiatry multi-disciplinary team (MDT) meetings, ward rounds, and informal gatherings.

> *"…that weekly [palliative care psychiatry multidisciplinary] meeting, like tomorrow I [psychiatrist] will discuss two new patients at that meeting with the broader team, and they [palliative care clinicians] just find that invaluable…it really up-skills them over time." (Psychiatrist 4)*

Optimising Referrals

Participants suggested a tiered approach for psychiatry referral, involving palliative physicians performing first-line depression care using low-burden structured methods or guidance from psychiatry, followed by psychiatry input if further assessment and management are needed. Participants voiced that the referral criteria for each discipline need to be tailored to clinicians' skills in individual local health services, including "deformalising" the referral processes to encourage earlier referrals.

> *"…to de-formalise [psychiatry referral criteria] and allow [palliative] clinicians to simply flag potential 'mood problems'. We found similar with delirium, many of our multi-D[isciplinary] team were reluctant to use the word 'delirium' verbally or in the case notes as they felt they hadn't 'diagnosed' it properly. However when we encouraged them to just flag 'confusion' or 'altered behaviour', [clinical service provision improved]… Perhaps a similar approach could work for depression." (Palliative Physician 4)*

Research-Level

Despite participants voicing mixed feelings about research in those with extremely short prognoses, all agreed that collaborative research between palliative medicine and psychiatry in studying various assessment and management options is pivotal.

> *"I think research are very important in our patient group and with the research then we'll be better guided on how we can manage these patients." (Palliative Physician 11)*

To overcome the feasibility and ethical concerns about enrolling patients with extremely short prognoses into experimental trials, modification of clinical trial designs was suggested (e.g., utilising pre-consenting method of consent or n-of-1 design).

> *"I'm interested in n-of-1 trials. I've seen them used for other medications. I think that could be something that could be applied to palliative care" (Palliative Physician 7)*

Society-Level

At the societal level, clinicians thought “rebranding” psychiatric interventions and services by making them part of the routine palliative care service provision might reduce the stigma of mental illness and enhance patient acceptance of psychiatric assessments and interventions.

> *“[We need to] rebrand psychiatry in oncology and palliative medicine, so that like in chronic pain, psychology is just part of your assessment, because it's normal to need a psychologist or psychiatrist as part of your team to help manage and get your optimal outcome in a very difficult situation” (Palliative Physician 2)*

6. DISCUSSION

This is the first study to capture palliative care physicians’ and psychiatrists’ practices and perceptions regarding depression care in people with prognoses of days to weeks. As the survey demonstrated, encountering depression in patients with extremely short prognoses was common. However, despite the high prevalence of depression (up to 50%) in this population and the frequency of clinical encounters, less than half of clinicians reported screening for depression, with all clinicians reporting uncertainty when assessing its cause.[305] They perceived depression care in this setting to be challenging and complex. In line with the literature, the initial survey found the perceived complexity arose from the interplay of multiple domains of challenges (Table 4.4):

- Patients’ frailty, co-existing symptom burden and associated end-of-life issues when time for intervention effects is poor[67, 112]
- Clinicians’ self-perceived limitations of psychiatry skills in the end-of-life setting with incompetence in diagnostic differentiation[67, 306-308]
- Inadequate resources and access to required interventions in local health services (e.g. mental health services)[67, 69]
- Heterogeneity of depression concept and the lack of evidence to guide practice in the literature for this context[305, 309]

- Unsupportive societal attitudes that prevents the optimisation of depression care (e.g. stigma of mental illnesses, the “normalisation” or “acceptance” of depression at the end-of-life).[306, 307]

The focus group discussions provided further details about the contributing challenges (Table 4.7), which were perceived to contribute towards the clinicians’ sense of nihilism.

Clinicians reported being less likely screen for depression and more ambivalent in depression assessment methods (e.g., approach to somatic symptoms of depression) in the extremely short prognosis setting compared to the better prognosis setting. Diagnosing depression in the setting of extremely short prognosis can be difficult because the symptoms of terminal illnesses (e.g., fatigue and weight loss) can confound the somatic symptoms of depression.[10] Importantly, this study shows that while clinicians may perceive somatic symptoms of depression to be less useful in depression diagnosis, somatic symptoms are still important to be considered during the overall depression assessment as they can affect the appropriateness of intervention choices. It may be desirable for clinicians to be trained with the various approaches to somatic symptoms such as Endicott Criteria to enable better diagnostic differentiation and depression assessment.[81]

While clinicians reported generally intervening less in this setting than among patients with better prognoses, it is worth noting the bimodal distributions of clinicians not using and more-likely-to-use certain non-typical pharmacological interventions (e.g., psychostimulants, atypical antipsychotics, benzodiazepines and novel medications such as ketamine) that have more augmentation and rapid-onset potential than typical antidepressants.[107, 230, 286, 310] This may reflect clinicians’ training - those aware of how to leverage the potential benefits of these non-typical treatments while minimising intolerance were more likely to embrace their use. In contrast, clinicians who lacked training or resources for these treatments did not tend to use them. Comparable to study findings in UK primary care and palliative settings, inadequately equipped clinicians may have a nihilistic attitude and ambivalence towards depression screening and assessment.[69, 306, 307] The low reported usage of ECT was likely related to

clinicians perceiving the intervention to be too burdensome for people with extremely short prognoses.[311] Consequently, clinicians and their MDT members should be given with the skills to screen, assess, and administer first-line rapidly effective depression interventions in a low-burden manner.[312] This may be facilitated by better linkage and integration of the psychiatry services into the palliative care services.[10, 281]

6.1 Inter-disciplinary Differences

6.1.1 Screening & Assessment Approaches

The finding that palliative physicians tended to use simple guided approaches (e.g., ultra-short screening tools) whereas psychiatrists undertook more detailed depression-specific assessments might reflect the different roles and skillsets of the disciplines: palliative physicians needing to cover a wide range of end-of-life issues with little psychiatry training; and psychiatrists requiring less guidance in depression care but may not be comfortable in dealing with associated end-of-life issues.[214] The concern raised during the palliative physicians' focus group discussions of *"robbing people of appropriate drivers"* for good closure with important persons at the end of life by treating depression highlights the challenges for palliative physicians in differentiating pathological depressive syndromes (for which interventions may improve social engagement) from appropriate reactive sadness, (in which offering interventions beyond psychosocial support may cause harm).[10, 313] While patients might be fearful about discussing their depression with treating clinicians, the results indicate that palliative physicians may also feel inadequately trained to initiate and effectively perform depression screening and assessment, perceiving these processes as time-consuming and burdensome for patients and themselves.[297, 313-317]

6.1.2 Management Approaches

While most clinicians used non-pharmacological interventions with these patients, palliative physicians were less likely than psychiatrists to use non-pharmacological interventions. These findings might reflect palliative physicians' perception of inadequacy, as found in the both the survey and focus group discussions, where during the focus group discussions they reported the

observation that inexperienced palliative physicians may consider more typical antidepressants instead of non-pharmacological interventions (e.g., dignity therapy) as foundation and adding rapid-onset pharmacological agents with psychiatry inputs (e.g., methylphenidate or ketamine) if indicated. In fact, palliative physician participants in the focus group discussions reported feeling inadequately trained and resourced to assess and respond to depression in the dying, not having rapidly effective therapeutic options available and not wanting to over-burden patients.

Meanwhile, the participating CL psychiatry cohort were skilled and experienced in treating patients with depression in this setting. Consistent with the literature, they perceived depression in advanced life-limiting illnesses to be potentially treatable, even in those nearing death.[10, 13, 107, 313] However, they acknowledged that they were a minority and felt under-resourced. This is echoed by the perception that psychiatrists who are skilled and experienced in palliative care are lacking, with some avoiding this field.[313, 315, 318] In fact, one previous psychiatry survey respondent reported *"Very few psychiatrists are comfortable working in the clinical space"* (Appendix 9). To improve care, there needs to be an increased awareness of the importance of palliative care psychiatry with funding prioritised.[281, 313]

6.1.3 Postulated Solution - Integration of Palliative Care and Psychiatry Care Processes

These observed differences between the clinical approaches of palliative physicians and psychiatrists highlight the need for better integration between palliative care and psychiatry in clinician training, health service delivery for improving supportive infrastructure (e.g., regulations towards methylphenidate prescribing), and research.[107, 214, 250, 313, 315, 319, 320] Similar to the United States palliative physician cohort, near 70% of the current survey's respondents expressed a desire for better collaboration with psychiatry services.[321] In fact, focus group participants regarded integrating palliative care and psychiatry processes as integral to facilitating consensus approaches to care, optimising access to needed interventions, overcoming the short-falls of both disciplines, and ultimately improving care for affected patients (Table 4.7).[10, 76, 214] These

postulated strategies are consistent with those suggested for improving palliative care and psychiatry collaboration in the general palliative care population.[215, 281, 322] While these strategies were postulated to facilitate consensus in approaches and leverage the strengths of both specialties, their effectiveness in improving outcomes for people with extremely short prognoses and the associated implementation barriers are yet to be determined.

6.2 Strategies and Implications

6.2.1 Provider Level

Adding routine depression screening to an established generic symptom screen in palliative care services (such as the PCOC SAS) may be helpful, though the optimal depression screening method in this extremely short prognosis subpopulation remains unknown.[76, 322, 323] Palliative physicians and psychiatrists should learn both psychiatric and palliative care skills relevant to this field.[297, 318] While evidence informing effectiveness of specific training strategies is scant in this setting, the postulated strategies reinforced by the literature include: informal education through integrative MDT meetings, clinics and ward rounds; and building formal integrative training opportunities such as joint educational seminars, clinical placement of trainees in the other specialty, and mandatory teaching in college training curricula.[214, 280, 281, 321, 322, 324] As postulated, training content may include skills that enable members of both disciplines to work collaboratively to deliver depression screening, assessment and management in a low-burden manner, and facilitating potentially effective psychotherapies as foundation (e.g., dignity and meaning-centred therapies), complemented by rapid-onset pharmacological agents (e.g., methylphenidate, and esketamine) as required.[10, 78, 107, 115, 215, 250, 280, 281, 315, 318, 320, 322, 325, 326]

6.2.2 Health System & Policy Level

The initial survey identified that palliative physicians perceived a lack of access to required psychiatric resources, despite Australasia having a well-resource health system by international standards (per capita).[297, 327] As found in the focus group discussions, a key contributor may be the lack of supportive infrastructure and inadequate liaison between existing palliative and psychiatric services.[313, 321] Health services need to prioritise efforts and fundings that

promotes palliative care and psychiatry service integration and timely depression interventions (e.g., funding for psychiatry presence and exemptions to regulatory restrictions for psychostimulants).[281, 313] As participants suggested, community volunteers can be trained to provide general emotional support or counselling to relieve the system burden.[328, 329] Furthermore, nurses and social workers from both disciplines can be trained to perform first-line depression assessment and deliver interventions for palliative care patients.[245, 322, 330, 331] In line with the postulated solutions, the treating palliative care team may be able to manage most depression cases after appropriate training, and referrals to psychiatry can be initiated when escalation of care is required.[10] The perspectives of various MDT members (e.g., nurses, pastoral care workers, and psychologists) and ways to leverage their strengths to deliver better care should be explored.

6.2.3 Research Level

While there is a paucity of palliative care psychiatry implementation studies to guide changes in this field, as perceived by participants, there lacks high-quality evidence of effective interventions when prognoses are poor.[91, 297, 332] Integrative palliative care and psychiatry research is needed. Randomisation, arguably, can be ethical if there is clinical equipoise (e.g., dignity therapy and methylphenidate trials).[107, 250, 332-334] Researchers need to consider innovative strategies to minimise burden and maximise potential benefits for participants. Feasibility studies prior to phase III trials and the use of alternative inclusive and supportive designs (e.g., pre-consent, n-of-1, and Bayesian response adaptive randomisation) warrant consideration.[233, 236] Using high-quality prospective case-control studies or modifying Naranjo criteria in phase IV pharmacovigilance study settings to imply causal relationship for interventions may also be possible.[238] Developing consensus approaches between palliative care and psychiatry via Delphi, and updating the existing guidelines based on the currently limited evidence to guide depression care specifically for people with extremely short prognoses need to be considered.[10, 76]

6.3 Study Limitations

6.3.1 Survey Limitations

The key limitation of this study was its low response rate, particularly from the RANZCP cohort. While this might be partially due the use of an online rather than paper-based survey,[335, 336] the current online survey response rates of 15% for ANZSPM and 0.03% for RANZCP (prior to the one reminder email sent to its Faculty of Consultation Liaison Psychiatry) were still lower than those of most other ANZSPM and RANZCP online surveys in recent years (averaging around 20%).[288-292] Potential reasons for this include: 1) clinicians focusing on COVID-19-related activities rather than research; 2) the survey being advertised at the bottom of the RANZCP's electronic newsletter (achieving a click rate of only 0.9% from the entire RANZCP cohort); and 3) the possible avoidance of or lack of interest in this topic (click rate of 5.2% from the Faculty of Consultation Liaison Psychiatry [600 members] despite placing the survey link directly in the reminder email). Therefore, the survey results might represent the viewpoints of a loculated cohort of palliative care physicians and psychiatrists, and may not be generalisable to non-Australasian clinicians. The low sample size also limited the power for detailed sub-group analyses. Intrinsic to the study methodology, there is a risk of reporting bias when the reported practices deviate from actual practices. Due to a technical fault, the survey question exploring psychostimulant use was initially unavailable to the first 28 ANZSPM respondents. Despite these limitations, the data collected still helped to inform the current practices and perceptions of some palliative care physicians and psychiatrists in Australasia. Lastly, while the prevalence data in Table 4.4 offer valuable insight into the prevailing perceived key barriers to and challenges of depression care in the extremely short prognosis setting among respondents, they do not necessarily reflect the hierarchy of importance or influence of these barriers towards depression care. In fact, the domain subcategories reported less often, such as the heterogeneity of depression concept and unsupportive societal attitudes, may reflect that many clinicians were not cognisant of these topics, suggesting the need to improve awareness of these issues.

6.3.2 Focus Group Limitations

The qualitative study's key limitation was the small number of focus groups conducted. As participants suggested, poor recruitment might have resulted from clinicians prioritising COVID-19-related clinical activities over non-COVID-19 research, avoidance by general (non-CL) psychiatrists due to perceived lack of relevance or interests, and the constrained ability of participating organisations in disseminating study invitations.[281, 315] Subsequently, recruitment expanded to include non-survey respondents. Meanwhile, maximum variation and data saturation may not have been reached, especially in the psychiatry cohort, and the differences found during comparison between palliative care and psychiatry cohorts is hypothesis-generating in nature.

7. CONCLUSION

Palliative physicians and psychiatrists perceived depression care in people with extremely short prognoses to be complex and challenging, with significant heterogeneity in the reported depression screening, assessment, and management approaches. The lack of clinician training, interdisciplinary collaboration, research, and supportive societal attitudes are likely contributors. Developing clinician training, supportive health infrastructures and innovative research strategies centred on integrating palliative care and psychiatry care processes may be helpful.

CHAPTER 5: SKIPMDD - SUBCUTANEOUS KETAMINE INFUSION IN PALLIATIVE CARE PATIENTS WITH ADVANCED LIFE-LIMITING ILLNESSES FOR MAJOR DEPRESSIVE DISORDER

1. PREFACE

The previous chapters describe research showing that while clinically significant depressive symptoms are prevalent in people with advanced life-limiting illnesses and extremely short prognoses, evidence to support effective interventions is scarce. Local Australasian palliative physicians and CL psychiatrists at the coalface reported significant challenges, including a sense of nihilism towards depression assessment and management in this context. Although most clinically significant depressive symptoms can be managed with non-pharmacological approaches, the first systemic review presented herein identified a sub-group of people with major depressive disorder for whom non-pharmacological therapy alone may not be effective. At the patient level, there is an urgent need to explore a feasible, tolerable and rapidly effective antidepressant for people with major depressive disorder when time pressure is high due to the extremely short life expectancy to ensure optimal quality of life at the end-of-life.

This chapter describes research into the possibility of conducting a future definitive clinical trial of ketamine as a rapid-onset antidepressant for people with major depressive disorder and extremely short prognoses. It reports a phase II feasibility study, and contains materials from an article published in BMJ Open in 2021 (protocol manuscript - Appendix 11) and another manuscript accepted for publication in PLoS One (2023 – in press), formatted to conform to thesis guidelines. The trial protocol is included as Appendix 12.

Lee, W., Sheehan, C., Chye, R., Chang, S., Loo, C., Draper, B., Agar, M., and Currow, D. (2021). Study protocol for SKIPMDD: subcutaneous ketamine infusion in palliative care patients with advanced life limiting illnesses for major depressive disorder (phase II pilot feasibility study). *BMJ Open*, **11**(6), e052312. (Citations: 3; Altmetric: 18)

Lee, W., Sheehan, C., Chye, R., Chang, S., Bayes, A., Loo, C., Draper, B., Agar, M., Currow, D. (2023). Subcutaneous Ketamine Infusion in Palliative

Patients for Major Depressive Disorder (SKIPMDD) – Phase II Single-arm Open-label Feasibility Study. *PLoS One.* (In Press)

2. INTRODUCTION

2.1 Current Challenges of Depression Treatment in Palliative Care

While non-pharmacological interventions are foundational to the treatment of depressive symptoms, for people with severe depressive symptoms non-responsive to these interventions, treatment options are few when prognosis is extremely short.[332] Despite typical antidepressants such as SSRIs and TCAs being more effective than placebo in the general palliative care population, most antidepressants have limited therapeutic benefits in this population due to the slow onset of actions (two to four weeks) and low efficacy.[112] It may take several trials of typical antidepressants (each trial taking around six weeks) for the efficacious antidepressant to be found for individual patients. Even on finding the "right" typical antidepressant, the remission rates of these typical monoamine-based antidepressants are as low as a third.[121, 337, 338] Ultimately, these clinically significant depressive symptoms reduce sufferers' ability to function and engage with others when quality time is critical.[2, 35] Therefore, there is a need for interventions that have rapid onset antidepressant actions that can act either as a sole therapy for those who have extremely short prognoses or as a bridging intervention while waiting for typical antidepressants to work.

Electroconvulsive therapy is used for treatment refractory depression in the general psychiatric population when all other conventional antidepressants fail.[339] It has a relatively fast onset of action (days to weeks) and is particularly effective in major depressive disorder with melancholic and psychotic features, achieving even greater reduction in depressive symptom severity than ketamine.[340, 341] However, its utility in the palliative setting can be low due to its invasive nature (requiring full anaesthesia and inducing seizures) and producing more neurocognitive impairment than ketamine.[287, 311, 340] Subsequently, ECT is rarely used by clinicians in the end-of-life setting.[297] Psychostimulants such as methylphenidate, which take effect in a few days, have been considered as alternatives to treat depression in palliative care.[108, 342-345] However, its

administration is generally restricted to the oral route, which is problematic for a large cohort of the palliative care population in the last days to weeks of life. [48, 342, 346-348]

2.2 Pathophysiology of Depression – A New Paradigm

Meanwhile, there is a growing literature suggesting that the pathophysiology of depression cannot be solely accounted for by the lack of monoamine (serotonin/noradrenaline), as once thought; certain sub-groups of patients are refractory to monoamine-based treatments, with less than a third of patients achieving remission.[121] Instead, there is emerging evidence that dysfunctional glutamatergic transmission may contribute to depression.[121] In particular, there is a decrease in brain extracellular glutamate, increasing N-Methyl-D-Aspartate (NMDA) and decreasing alpha-amino-3-hydroxy-5-methyl-4isoxazeolepropionic acid (AMPA) neurotransmission.[349] This is thought to lead to a lack of neural plasticity and synaptogenesis, impairing emotion and cognition.[121]

2.3 Ketamine and Depression – Psychiatry Literature

Ketamine is a non-competitive NMDA receptor antagonist. Historically, it has been used predominantly for its anaesthetic and analgesic effects, even in patients with advanced life-limiting illness.[130-134] It modulates central sensitisation and produces dissociation symptoms by direct action on the cortex and limbic system.[350-352]

In the psychiatry literature, there is growing evidence that sub-anaesthetic doses of parenteral ketamine can act as an effective rapid-onset antidepressant for patients with treatment resistant major depression who have failed monoamine-based therapies.[135-144] It is thought that sub-anaesthetic doses of ketamine rapidly and transiently increase extracellular glutamate level in the brain. This leads to an increase in AMPA receptor activation and increase BDNF brain derived neurotrophic factor (BDNF) in the prefrontal cortex and the hippocampus. Subsequently, synaptogenesis and neural plasticity increase, theoretically causing the antidepressant effect.[353]

The onset of antidepressant effect can be as rapid as two hours after a parenteral infusion of ketamine, with its effect lasting up to one week as a single-bolus dose, or 12 weeks as repeated boluses.[136, 139-143, 353, 354] The

response rate has been as high as 70%, with the number needed to treat as low as three in a meta-analysis.[138, 139, 141] While its efficacy against treatment resistant depression is inferior to ECT, the effect size is still remarkable - better than typical antidepressants.[340, 341] Nonetheless, the short duration of antidepressant action and the high relapse rate after a single dose of ketamine are important limitations.[200, 355, 356] No serious adverse effects in the psychiatric population, who are generally younger and have fewer co-morbidities than the palliative care population, have been reported.[135, 137, 142, 143] Many researchers have reported transient psychotomimetic and dissociative symptoms,[135, 136, 142, 143] and some showed these symptoms could be resolved within four hours of administration.[142-144] Ketamine, thus, may be a rapidly effective and well-tolerated treatment for major depression in the palliative care setting, or a bridging intervention employed while waiting for typical antidepressants to work.

2.4 Potential Challenges for Running Ketamine Trials in the Palliative Care Setting

Despite the emerging evidence of ketamine's effectiveness as an antidepressant in the psychiatry population, high-quality prospective ketamine trial data for major depressive disorder in the palliative care setting is lacking. The literature includes case reports of intramuscular and intravenous ketamine, open label proof-of-concept trials using oral and intranasal ketamine, and a retrospective study (Iglewicz et al., 2015) demonstrating the effect of ketamine on depression in patients receiving hospice care.[136, 357-360] However, there is yet to be an RCT of ketamine treatment for major depressive disorder in the palliative care population, let alone those with prognoses of days to weeks.

The lack of high-quality prospective ketamine trials in the palliative care setting has several possible explanations. One might be the difficulty of conducting clinical trials in the palliative care population, particularly in people with extremely short prognoses.[63, 361] As illustrated in Chapter 4, there are feasibility, tolerability and ethical concerns about palliative patients participating in clinical trials, particularly towards the end of life when quality time are considered precious.[362] Patients' rapidly progressive medical illnesses imply a high attrition rate. Depressive symptoms might further reduce their interest in participating in

a trial and their capacity to consent to research participation. The pharmacokinetics of ketamine are not well understood in people with significant organ dysfunction in the palliative care setting, raising tolerability concerns if the conventional psychiatry dosing of 0.5mg/kg were to be administered.[138] At the health system level, the challenges faced by palliative care clinicians in caring for depression in those with extremely short prognoses (e.g., the lack of routine depression screening and the inadequate clinician training and supportive health system) compounds the difficulty in involving patients in clinical trials.[362] There might be clinician resistance towards the use of parenteral ketamine in the palliative care population, especially after a clinical trial showing significant neurocognitive side effects of ketamine (likely psychotomimetic and dissociation symptoms) when given parenterally for pain management at dosages of 100-500mg/day.[134] There were also ethical concerns about palliative participants missing out on potentially effective antidepressant treatments if enrolled in trials with restrictive designs, limiting the use of other treatments.[362] From a research trial design perspective, the lack of understanding of the duration of ketamine's potential antidepressant effects means that there might be a prolonged washout period if a cross-over design is used, which may not be feasible if the prognoses of patients are extremely short.

Given the concerns above, it is questionable whether conducting a phase 3 RCT using ketamine as a rapid onset antidepressant in this population is feasible. Prior to proceeding to a phase 3 trial, a feasibility study is needed.

2.5 Possible Solution - Ultra-low Subcutaneous Ketamine Infusion with Individual Dose-Titration Design

In 2016, Loo et al.[230] published evidence that the efficacy of subcutaneous bolus of ketamine is non-inferior to the conventional intravenous 40-minute infusion route in treating depression, while producing a better tolerability profile. This supports the use of subcutaneous ketamine in the palliative care population. This route is also the preferred route of medication administration in the palliative care setting, because many patients, towards the end of life, cannot swallow effectively but do not want intravenous administration due to discomfort.[48, 348] Furthermore, Loo et al.'s study[230] shows that ketamine has

antidepressant activity at dosages even less than the conventional 0.5mg/kg, and can be given via individual titration on repeated weekly dosing from 0.1mg/kg to 0.5mg/kg to maximise tolerability.

Additionally, in the psychiatric population with relatively normal organ function, increasing the duration of intravenous ketamine infusion from 40 to 100 minutes may produce similar antidepressant effectiveness with better tolerability.[363, 364] Given the prevalence of abnormal baseline renal and liver function in the palliative population, it is arguable that the antidepressant activity could be maintained with a ketamine infusion over two hours.[365, 366] This is also supported by the acute and cancer pain literature, which demonstrates the sparing of psychotomimetic effects if ketamine is started at a rate equivalent of 0.1-0.2mg/kg over two hours, titrate up to response up to a rate equivalent of 0.6mg/kg over two hours for a 40kg person.[131-133, 367] Therefore, it is postulated that the use of an individual dose-titration method of subcutaneous ketamine infusion over two hours for major depressive disorder starting at 0.1mg/kg is feasible and worth exploration.

Not only is there a need to assess short-term response to ketamine (within a week), but there is also a need to understand the medium-term response (within weeks) to ketamine in palliative care patients, which is poorly understood at present. This would potentially allow ketamine to be used to treat major depressive disorder in palliative patients, especially those with extremely short prognoses, and for ketamine to considered as a bridging therapy for those whose severity of depression requires immediate intervention to prevent harm while waiting for the clinical benefits of typical antidepressants if the patients live longer.

2.6 Phase II Feasibility Study

The feasibility study described in this article investigated the feasibility, safety, tolerability and activity/signal of ketamine for major depressive disorder in a population with advanced life-limiting illnesses, inclusive of individuals with extremely short prognoses, prior to researchers committing to a larger phase III study. In particular, the following were explored:

- Recruitment feasibility, demonstrated by the number of individuals with advanced life-limiting illnesses and major depressive disorder who would participate in and subsequently complete various stages of the trial

- The safety, tolerability and activity of sub-anaesthetic doses of subcutaneous infusions of ketamine at doses up to 0.4mg/kg in patients with advanced life-limiting illness

3. AIMS, OBJECTIVES AND HYPOTHESIS

3.1 Aim

The aim of this study was to determine the feasibility, safety, tolerability, acceptability and activity of individually tailored subcutaneous ketamine as a treatment for major depressive disorder in patients with advanced life-limiting illnesses to inform a larger phase III trial.

3.2 Objectives (endpoints)

The primary objective of this study was to determine the feasibility of ketamine subcutaneous infusion for major depressive disorder in the palliative setting, measured by the numbers of consented patients who were screened, treated with ketamine and completed the various study stages.

Secondary objectives were to determine the safety, tolerability, acceptability and activity of the treatment using an individually tailored dose-titration approach, based on the:

- Frequency and severity of psychotomimetic (Brief Psychiatric Rating Scale [BPRS]) and dissociative symptoms (Clinician-Administered Dissociative State Scale [CADSS])
- Frequency and severity of general adverse events (National Cancer Institute Common Terminology Criteria for Adverse Effect 4.0 - NCI CTCAE 4.0)
- Numbers of participants with improvement in symptoms of depression assessed with the Montgomery-Asberg Depression Rating Scale (MADRS) at measured time points over the study period
- Pain (Numeric Pain Rating Scale [NPRS])

- Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)
- Reasons potential participants are unable to complete each of the study stages
- Participant's satisfaction of ketamine as an antidepressant and the SKIPMDD trial process (2-item questionnaire)
- Associations between baseline characteristics and clinical outcomes

3.3 Hypothesis

Subcutaneous ketamine, administered as a 2-hourly dose-titration infusion on a weekly basis, is a feasible, safe, acceptable, and tolerable method of rapidly reducing the severity of major depressive disorder in palliative patients with advanced life-limiting illnesses.

4. METHODS – STUDY DESIGN AND JUSTIFICATIONS

Reporting of the protocol section of this study is compliant with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline.[368] The other parts of this study is reported according to the Consolidated Standards of Reporting Trials (CONSORT) Extension for Randomised Pilot and Feasibility Trials **C**hecklist.[369]

4.1 Study Design

The study was a phase II multicentre feasibility study. It had an open-labelled, individual dose-titration design, with all participants receiving subcutaneous ketamine infusions. The rationale for this design is discussed below.

4.2 Population & Eligibility Criteria

The target population was patients with advanced life-limiting illnesses and major depressive disorder being treated in the acute hospital, palliative care units, and the community of the following Australian palliative care services: Liverpool Hospital, Braeside Hospital, Calvary/St George Hospitals, and Sacred Heart/St Vincent's Hospital, in Sydney, Australia. The inclusion criteria were: 1) adults (≥18-year-old); 2) known to palliative care services with palliative intent of treatment for irreversible life-limiting illnesses; 3) Patient Health Questionnaire-2

(PHQ-2) score ≥ 3 on screening; 4) Major depressive disorder diagnosed by Endicott Criteria (Table 5.1) diagnosed by trained personnel;[23, 81] 5) Clinically significant depression severity defined by Montgomery-Asberg Depression Rating Scale (MADRS) Depression Severity Score ≥ 16; 6) willing and able to comply with all study requirements; and 7) signed, written informed consent for the study.

The exclusion criteria were:

- AKPS score = 10
- Methylphenidate use in the last four weeks
- Changes in anti-depressant doses in the two weeks before the commencement of ketamine
- Ketamine use in the previous four weeks
- Previous significant adverse effect or hypersensitivity to ketamine
- Concurrent phenobarbitone use
- Factors of increased risk of intracranial pressure:
    i. Recent ischaemic or haemorrhagic cerebral vascular accident in the last one month
    ii. Brain tumours with symptoms and signs of increased intracranial pressure
    iii. Seizure in the last six months
    iv. Head trauma with symptoms of increased intracranial pressure
    v. Hydrocephalus
    vi. Uncontrolled nausea, vomiting and headache (e.g. from cerebral metastases, trauma), ≥ grade three nausea despite one line of antiemetics
- Factors of increased risk of sympathomimetic response (hypertension and tachycardia) with associated complications
    i. Uncontrolled hypertension with systolic blood pressure ≥ 160
    ii. Tachycardia with heart rate ≥ 120 per minute.
    iii. Symptomatic ischaemic heart disease (e.g. exertional angina) and decompensated heart failure with NYHA class III and IV symptoms
    iv. Uncontrolled hyperthyroidism (Low TSH with high T3 and/or T4)

v. Diagnosis and history of porphyria

- Factors of increased risk of intraocular pressure with its complications
  i. Glaucoma
  ii. Open eye injury / Acute globe injury
- Severe hepatic impairment: bilirubin ≥ three times upper limit of normal; AST and/or ALT > five times upper limit of normal - clinically determined to be due to hepatic impairment
- Severe renal impairment (Creatinine clearance <15ml/min by Cockroft Gault Equation)
- Other mental disorders apart from major depression (lifetime history schizophrenia/bipolar/mania)
- Recent substance misuse as determined by the treating and research clinicians

The PHQ-2 was used to screen for major depressive disorder in the palliative care population, minimising the burden of administration to participants while maintaining high sensitivity and specificity.[78, 370, 371] This was followed by a diagnostic interview using Endicott Criteria. The substitute approach was to replace the four somatic items of DSM-IV criteria with other more depression specific items, potentially reducing the chance of misattribution of the symptoms of terminal illness as major depressive disorder.[15, 81, 372, 373] Although DSM-5 was available, the psychometric properties of Endicott Criteria have not been established using DSM-5 in the oncology population.[374] The MADRS score was used to assess depression severity. This tool has been widely used and accepted as a standard to measure the anti-depressant response of ketamine in the psychiatric literatures.[142, 230, 375-377] A usual cut-off of MADRS ≥ 20 indicates moderate severity depression.[142, 230, 375-377] Nonetheless, the inclusion criteria of this study were broadened to include depression of milder severity. It was thought that ketamine may still benefit participants with milder depression when prognoses are too short for meaningful effectiveness from the typical antidepressants. Consequently, the threshold of MADRS ≥ 16 has been selected in this protocol to ensure participants with clinically significant

depressive symptoms were recruited, in congruence with Pezzella et al. (2001).[378]

TABLE 5. 1. DSM-5 SYMPTOMS OF MAJOR DEPRESSIVE DISORDER AND ENDICOTT SUBSTITUTE SYMPTOMS (ENDICOTT CRITERIA)[4, 81]

DSM-IV Symptoms	Endicott Substitute Symptoms
Depressed mood most of the day*	
Marked diminished interest or pleasure in all, or almost all, activities most of the day (Anhedonia)*	
Weight loss or gain (>5% body weight in a month) / change in appetite	Depressed appearance
Insomnia or hypersomnia	Social withdrawal or decreased talkativeness
Psychomotor agitation or retardation	
Fatigue or loss of energy	Brooding, self-pity or pessimism
Feeling of worthlessness or excessive or inappropriate guilt	
Diminished ability to think or concentrate, indecisiveness	Lack of reactivity; cannot be cheered up
Recurrent thoughts of death, or suicidal ideation or planning, or a suicide attempt	

*One of these symptoms must be present for a diagnosis of major depressive disorder. Each symptom must also meet severity criteria of “most of the day” or “nearly every day” with a duration of greater than two weeks. The symptoms must cause clinically significant distress or impairment. They are not due to a physiological effect of a medication or general medical condition, and must not be accounted for bereavement. These symptoms are not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders. There has never been a manic episode or a hypomanic episode.

Palliative trials of ketamine generally have a stringent set of exclusion criteria, excluding conditions commonly encountered in the palliative setting (e.g., cardiac failure and intracerebral mass). The thresholds of many exclusion criteria were based largely on physician’s assessments rather than absolute values.[132-134] However, absolute thresholds for some of these exclusion criteria

were set for reproducibility. To assimilate the clinical population who often have significant organ dysfunction and comorbidities, efforts were made to ensure that the exclusion criteria were relatively inclusive, as shown above. Some examples include: setting a very low score of AKPS of 10 as an exclusion criterion; not excluding individuals with brain metastases unless there were concurrent symptoms or signs of increased intracranial pressure; lenient exclusion criteria for systolic blood pressure and pulse rate; and only excluding individuals with severe hepatic and renal impairments defined according to the National Cancer Institute-sponsored Organ Dysfunction Working Group[379, 380] and American Society of Clinical Oncology for Anti-cancer Therapies[381] respectively. The renal impairment exclusion has been lowered to exclude only those with a creatinine clearance of <15ml/min, given the ultra-low initial dose (0.1mg/kg over two hours) of ketamine and the mild effects of its active metabolite on renal function.[382] The exclusion of ketamine use in the last four weeks was chosen because ketamine's anti-depressant effect might last that long.[353]

4.3 Interventions

The study intervention involved the initial subcutaneous infusion of 0.1mg/kg ketamine over two hours. If there was a lack of response from the previously administered dose, dose could be escalated at 0.1 mg/kg increments weekly (Figure 5.1). Participants were allowed up to four doses (four weeks), with a maximum dose of 0.4mg/kg. After this treatment phase, participants were monitored for another four weeks, giving a total of eight weeks of observation.

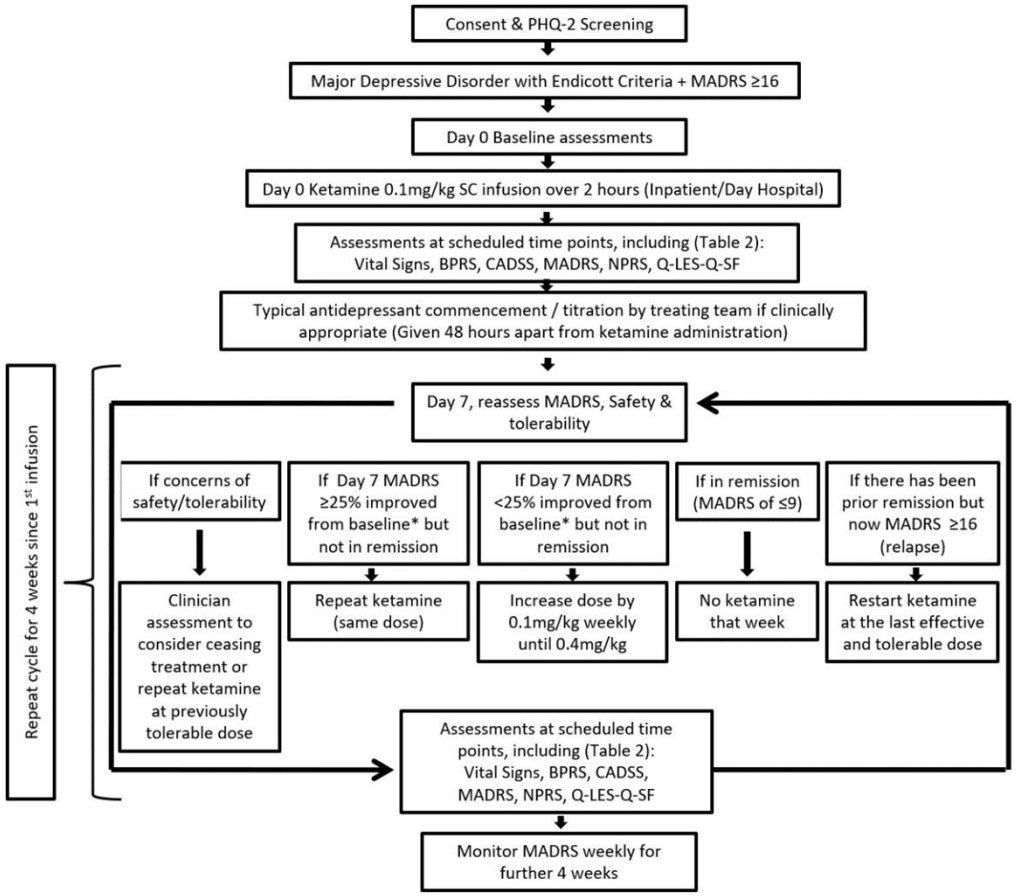


FIGURE 5. 1. SKIPMDD STUDY PROCEDURE

Abbreviations: BPRS, Brief Psychiatric Rating Scale; CADSS, Clinician Administered Dissociative States Scale; MADRS, Montgomery-Asberg Depression Rating Scale; NPRS, Numeric Pain Rating Scale; PHQ-2, Patient Health Questionnaire-2; Q-LES-Q-SF, Quality-of-life Enjoyment and Satisfaction Questionnaire—Short Form. *Baseline MADRS score is the MADRS score prior to the last ketamine dose (default) if relapse (MADRS of ≤9) has not occurred. if relapse has occurred, the MADRS score at relapse becomes the baseline.

The subcutaneous route of administration was chosen because it yields comparable efficacy to the conventional intravenous infusion and results in less cardiovascular, psychotomimetic, and dissociative side effects.[230, 231] This is possibly related to the halved peak plasma concentration associated with the subcutaneous route, compared to the intravenous route.[230] The use of slow infusion rather than boluses may further minimise the risk of toxicity. Reports have shown that intravenous ketamine infusions over 100mins exhibited less toxicity than the standard infusion over 40mins with comparable antidepressant effect.[363, 364] Additionally, the psychotomimetic effects might be spared if

ketamine is commenced at ultra-low dose infusion equivalent to 0.1-0.2mg/kg per hour, even in the cancer setting.[131-133, 367] Since prior studies have shown that participants' responses were observed at doses below 0.5mg/kg, the individually tailored dose-titration approach was implemented.[230, 231, 377] In addition, a weekly dosing interval was scheduled, because the peak response to ketamine may take up to three days to occur.[143, 377]

After the initiation of ketamine infusion, if deemed appropriate for the participant's clinical needs (e.g., for neuropathic pain titration), a typical anti-depressant of choice at the discretion of the treating clinician could be commenced or have its dose changed 48 hours apart from the ketamine administration. There was a concern regarding the confounding antidepressant effect from allowing the introduction of or dose change in the typical antidepressants during the study. However, to comply with human research ethics requirements, the enrolled participants could not be denied from the benefits of typical antidepressants while participating in the trial, especially when the prognosis was uncertain. Furthermore, the participation could not reduce their physical symptom control (e.g., restricting typical antidepressants dose-titration for managing neuropathic pain or anorexia).[109, 224] Given the slow onset of action of the typical antidepressant (i.e. ≥ four weeks),[112] and the contrasting rapid onset and offset effects of ketamine (within days), the antidepressive effect of ketamine may still be differentiated from that of the typical antidepressant.[135-144, 230, 363, 364, 383] Additionally, the minimum of 48 hours interval set between the administration of a typical antidepressant and ketamine infusion allowed for better recognition of the potential adverse effects of ketamine, which likely occur within hours of infusion and last less than a day.[144, 230]

To determine the short-term (< one week) and medium-term (one to eight weeks) responses to ketamine, this study included a four-week ketamine administration period and another four-week follow-up period. This duration was chosen as a balance between acquiring adequate short- and mid-term safety and efficacy data and maintaining the study's feasibility with a potentially high

attrition rate, which was expected due to the progressive nature of terminal illnesses.

4.4 Comparator

A control arm was not included because the primary research question was about feasibility. Having a control arm might further lower the study feasibility.

4.5 Outcome Measures

The primary outcome was feasibility, measured as absolute numbers (including accrual rate of multiple centres) and proportions of palliative care patients who consented, were screened for major depressive disorder, met the study eligibility criteria, were treated with subcutaneous ketamine, followed up and completed the study. A priori “stop-go” criteria for the future definitive study were set. The use of individually tailored dose-titration subcutaneous ketamine will be worthy of evaluation in the future definitive study if:

- The steady-state recruitment rate is 1.25 participants per month or higher up to 24 months, but not if it is 0.5 participants per month or lower; and
- The proportion of treated participants with a positive response (≥50% reduction in MADRS score) in symptoms is 30% or higher, but not 10% or lower.

Secondary outcomes and endpoints that correspond to the secondary objectives were listed according to the various assessment time points in Table 5.2. For measuring side effects and tolerability, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)[384] was used to measure the general non-psychiatric adverse events. The participating sites’ familiarity with its use from running the previous ketamine trial for pain was thought likely to expedite the detection of potential adverse events in this vulnerable population.[134] Nonetheless, NCI CTCAE[384] was unable to capture the psychotomimetic and dissociative symptoms of ketamine comprehensively. The standard tools of Brief Psychiatric Rating Scale (BPRS),[385, 386] Clinician Administered Dissociative States Scale (CADSS),[387, 388] and MADRS[389] were used for consistency with the ketamine studies in the psychiatry literature.[139, 142,

[230, 231, 356] Positive antidepressant response was defined as a MADRS score reduction of ≥ 50% from baseline and remission as MADRS score ≤9.[144, 230] Relapse was defined as MADRS ≥ 16 after a remission. The time points for MADRS measurements were chosen to capture the initial time to response (as little as six hours), the time to maximal response (usually between one to three days), and the duration of response (averaging around seven days).[136, 139-143, 231, 353, 354] Since the MADRS depression score may be affected by uncontrolled pain, concurrent pain level was assessed using Numeric Pain Rating Scale (NPRS), and the correlation between these factors explored.

4.6 Trial Status

This trial was registered in the Australian New Zealand Clinical Trial Registry (ACTRN12618001586202). Recruitment commenced on the 29th of July 2019. Due to the COVID-19 pandemic, the trial was suspended for various durations at all sites on the 24th of March 2020, and gradually recommenced at different sites with all sites recruiting on the 17th of August 2020. The total durations of the trial opening at various sites were: Liverpool – 13 months; Braeside – 21.5 months; Sacred Heart/St Vincent's Hospital – 21 months; and Calvary Hospital – 19 months. The trial was closed on the 27th of Oct 2021.

4.7 Consumer Involvement

Consumers were involved in the interpretation and discussion of the study results to aid planning for the future definitive trial.

4.8 Study Procedure

The study procedure is illustrated in Figure 5.1. It was overseen and coordinated by the Australian Palliative Care Clinical Studies Collaborative (PaCCSC) Trial Management Committee (TMC). The TMC consists of chief study investigators and key members of the PaCCSC group not involved in this study. They oversaw trial governance through PaCCSC Standard Operating Procedures, providing the infrastructure for data collection, management, analysis, and monitoring.

Under the guidance of BD and CL (psychiatrists), the coordinating principal investigator, WL, was trained to perform psychiatric assessments. WL then

provided site initiation and ongoing training to the rest of the research team (study nurse, site coordinator, and investigators).

Although screening for depression has been recommended in the palliative population due to its high prevalence, [10, 12, 305] screening was not yet a routine practice at participating sites. Therefore, it was an ethical requirement to obtain consent from potential participants before screening for major depressive disorder and assessing eligibility criteria.

As patients with major depressive disorder may have impaired capacity to provide consent, research clinicians used the MacArthur Competence Assessment Tool for Clinical Research to assess and confirm capacity to consent.[277, 278, 390] Due to feasibility concerns over the use of this tool in those with significant frailty and symptom burden, rather than using the full 21-item assessment tool, the four overarching principles of the assessment tool in assessing consent capacity were used: understanding; appreciation; reasoning; and expressing or evidencing a choice.[277, 278, 390] Only individuals who were able to provide informed consent were included.

Eligible participants then underwent four weeks of ketamine treatment (Week 1-4). During this period, the participants' responses to ketamine were regularly monitored on a pre-determined schedule (Table 5.2). The day-7 response (MADRS score and tolerability) determined the subsequent titration of ketamine dosing (Figure 5.1). After the initial four weeks, the participants then entered the follow-up phase, in which they were monitored weekly (Week 5-8). Given that no long-term safety data on ketamine use as an antidepressant in the palliative care population were available, there was no ongoing provision of ketamine for depression after the study.

TABLE 5. 2. ASSESSMENT SCHEDULE

Assessments	Eligibility	Baseline (t0 min)	30 min	1hr	1.5hr	2hr (infusion complete)	4hr	6hr	1 day	2 days	3 days	7 days	Weekly (day 7) if no repeat ketamine infusion (up to 8 weeks from initial dose)
Informed consent	**X**	**X** (Re-affirm)											
PHQ-2	**X**												
Endicott Criteria	**X**												
AKPS	**X**	**X**							**X**	**X**	**X**	**X**	**X**
Vital Signs		**X**	**X**	**X**	**X**	**X**	**X**	**X**					
ECG		**X**											

Assessments	Eligibility	Baseline (t0 min)	30 min	1hr	1.5hr	2hr (infusion complete)	4hr	6hr	1 day	2 days	3 days	7 days	Weekly (day 7) if no repeat ketamine infusion (up to 8 weeks from initial dose)
Bloods (FBC/LFT/EUC /TFT)	X												
MADRS[389]	X	X						X	X	X	X	X	X
BPRS[385, 386]		X				X	X	X					
CADSS[387, 388]		X				X	X	X					
NPRS[391, 392]		X						X	X	X	X	X	X
Adverse Events (NCI CTCAE 4.03)[384]		X	X	X	X	X	X	X	X	X	X	X	X
Q-LES-Q-SF[391, 392]		X									X	X	

Assessments	Eligibility	Baseline (t0 min)	30 min	1hr	1.5hr	2hr (infusion complete)	4hr	6hr	1 day	2 days	3 days	7 days	Weekly (day 7) if no repeat ketamine infusion (up to 8 weeks from initial dose)
Concomitant medications		**X**									**X**	**X**	**X**
SKIPMAJOR DEPRESSIVE DISORDER Participant Satisfaction Questionnaire													**X (only at the end of the study – study completion or withdraw)**

Abbreviations: AKPS - Australia-modified Karnofsky Performance Scale; BPRS - Brief Psychiatric Rating Scale; CADSS - Clinician Administered Dissociative States Scale; ECG – Electrocardiogram; EUC – Electrolyte Urea Creatinine; FBC – Full Blood Counts; LFT – Liver Function Test; MADRS - Montgomery-Asberg Depression Rating Scale; NCI CTCAE - National Cancer Institute Common Terminology Criteria for Adverse Events; NPRS -Numeric Pain Rating Scale; PHQ-2 - Patient Health Questionnaire-2; Q-LES-Q-SF - Quality-of-life Enjoyment and Satisfaction Questionnaire - Short Form; SKIPMDD - Subcutaneous Ketamine Infusion in Palliative Care Patients with Advanced Life Limiting Illnesses for Major depressive disorder; TFT – Thyroid Function Test

Investigators reported any Serious Adverse Event to the PaCCSC Trial Coordinating Unit, which liaised with the assigned medical monitor (given this was a feasibility study, a medical monitor rather than the data monitoring committee was used). When appropriate, the Human Research Ethics Committee was to review the safety information of ketamine. The investigators would stop the study if adverse event reporting indicated safety concerns.

Each participant was allocated a unique identification number. All trial data was recorded on the study case report forms and entered by the research nurses into REDCap - a centralised electronic database protected via Secure Sockets Layer encryption.[393] All source documents and the master list linking identifying participant information and identification numbers were stored in a locked cabinet at each site. All information was only accessible to those conducting the study. There was no anticipated sharing of data past the investigator group.

Study records will be maintained for 15 years after study completion in secure archiving facilities in compliance with National Health and Medical Research Council and the Good Clinical Practice guidelines.[303, 394] Data confidentiality, accuracy and protocol compliance were monitored by members of TMC or their delegates, audited on an ad hoc basis. The study was also subject to inspection by regulatory bodies (e.g., Therapeutic Goods Administration).

4.9 Data Analysis

A formal conventional power and sample size calculation was not required due to the feasibility focus of this study, as the study results would inform such for the future definitive trial.[395, 396] Nonetheless, for operational considerations, recruitment for up to two years or a sample size of up to 32 was used as the stopping criterion (assuming a conservative effect size of 30%, comparable to that of the typical antidepressants, and an one-sided confidence interval of 80%).[397, 398]

The primary analysis concentrated on the feasibility metrics and adherence outcomes, which were analysed with frequencies and percentages. The change of assessment score from baseline for side effects, tolerability, and efficacy data were analysed: percentage change for MADRS; and absolute change for

BPRS, CADSS, Q-LES-Q-SF, and haemodynamic observations. Data were analysed with descriptive statistics without inferential statistics or formal hypothesis testing.[396] Normally distributed data were summarised with mean and standard deviations, and non-normal data with medians and interquartile ranges. Statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA). Associations for total MADRS and MADRS without somatic items with pain score (NPRS) were assessed using Kendall's tau from day 1 to day 7. The exact significance levels for Kendall's tau were used with a permutation test, given the small sample size ($n < 10$).

4.10 Ethical Considerations and Dissemination

This study was approved by South Western Sydney Local Health District (reference number: HREC/18/LPOOL/466) on the 18th of February 2019. Minor administrative amendments were approved on the 9th of February 2021 (protocol version 1.3). The results of this study were submitted for publication in peer-reviewed journals and presented at relevant conferences.

4.10.1 Minimising Harm for the Vulnerable Population

Individuals with major depressive disorder and advanced life-life limiting illnesses are a vulnerable population. Hence, the study objectives and design were finessed in ways that reduced harm while maximising potential benefits. There was no deception of participants in this study. Each interaction with the participants was undertaken by carefully selected and trained study staff. This training was initially undertaken in conjunction with palliative care physicians and psychiatrists and senior research personnel involved in the research team, all trained in Good Clinical Practice.

4.10.1.1 Minimising the Risk of Physical Harms

The study measures were carefully selected to ensure the provision of the best possible data with the least impact and burden on the participants. The study questionnaires were, validated in the setting of advanced life-limiting illnesses, and as concise as possible. The only invasive test was the blood test performed for eligibility and to ensure participant’s safety (e.g., to minimise the risk of adverse reactions from study intervention in the setting of severe liver

impairment). Meanwhile, the number of blood tests was minimised by deeming them unnecessary if tests within the previous four weeks was available and the clinical picture for the potential participants had not changed within that time.

The assessment timepoints were carefully planned to ensure that attentive symptom monitoring for both beneficial effects and potential adverse reactions of ketamine did not over-burden participants. This allowed clinicians to respond to any potential adverse effects in a timely manner.

To minimise the risks of adverse effects, the researchers used subcutaneous infusion, which has been shown to be the most predictable and best tolerated route.[230, 376, 399] Accounting for how ill these participants were (with organ dysfunction and consequent impaired ketamine metabolism and clearance), not only were specific exclusion criteria set more rigorously than in the previous ketamine for cancer pain trial,[134] but the individual dose titration method devised by Loo et al. (2016) was used.[230] Ketamine was started at the ultra-low dose of 0.1mg/kg and titrated up to effect to a maximum of 0.4mg/kg according to participants' tolerance and anti-depressant response.[230] This is less than the conventional ketamine dose of 0.5mg/kg in the psychiatry literature, thus reducing the risk of adverse effects in the context of potentially altered drug metabolism and clearance due to advanced life-limiting illnesses.[366] Through modifying the route from intravenous to a subcutaneous ketamine infusion method, the risks of the participants experiencing injection site reaction or transient cardiovascular side effects (< 90 minutes duration) were low.[144, 230]

4.10.1.2 Minimising the risk of Psychological Distress

There was a concern about whether ketamine, like other typical antidepressants, transiently increases suicidality due to the reduction of psychomotor retardation occurring prior to improving the subjective mood. Not only has there been no evidence of ketamine administration causing increased suicidality,[399] ketamine has been shown to reduce suicidality in the otherwise well treatment-resistant depression population with an onset as fast as 40 minutes, lasting for several days.[376] Nevertheless, the MADRS suicidal ideation

item was administered frequently (four times a week after ketamine infusion) to ensure prompt recognition of worsening suicidality.

Participants might experience transient psychotomimetic symptoms, which might cause psychological distress. However, these symptoms were found to be mild in a systematic review when given intravenously over 40 minutes, and were not found to persist beyond four hours of infusion.[144] Given subcutaneous infusions over two hours starting at ultra-low dosages were administered, the risk of psychotomimetic symptoms was even lower. Should there be psychological distress due to psychotomimetic symptoms, participants would be supported through the presence of staff and carers until the symptoms subsided, and rescue medications (e.g., midazolam) used if necessary.

Some participants could experience distress when completing study measures, because the assessment of mental state includes discussion of mental health and quality of life that participants might find distressing (e.g., social withdrawal or suicidal ideation). Any distress would be ameliorated by the research staffs and members of the palliative care MDT (including clinicians, pastoral care workers, social workers, and psychologists) who were trained in supportive communication strategies. Should the emotional distress remain significant, the treating palliative care team would consult the local mental health team for further input.

4.10.2 Research on People in Dependent Relationships

Potential participants might feel that they were in a dependent position in the doctor-patient relationship, and thus pressured to engage with the trial.[400] The research team worked to minimise any possibility of undue influence. For example, the study was presented to the potential participants by the palliative care service and the research team in as unbiased a way as possible, separating the usual clinical care from the research tasks. Research personnel not directly involved in the clinical care of the participants acquired informed consent, which was re-affirmed prior to the commencement of ketamine administration. Participants were regularly informed that they were able to withdraw from the study at any time without their clinical care being affected.

4.10.3 Discrimination, Stigma or Other Social Harm

Ketamine, like several other palliative care medications (e.g., opioids), has the potential for abuse.[401] Participants on the trial might feel concerned about being stigmatised as drug users in their own social circles. Therefore, the study intervention (ketamine) was administered only within a hospital environment; no medication was provided to take home. This was designed to minimise risks of social harm and discrimination associated with ketamine use.

4.10.4 The Possibility of Researchers Experiencing Psychological Distress

Research team members who had direct contact with depressed participants could experience depressive symptoms due to transference, and feel powerless and/or hopeless.[362, 402] Prior to contact with participants, research team members were given training with the input of the psychiatry investigators to help staff members engage with depressed participants. Regular debriefing sessions were undertaken at local sites to ensure that research team members were well supported. Members were informed that should they feel significant distress, they should seek medical and psychological advice through their trusted general practitioner, counsellor, psychologist or psychiatrist.

5. RESULTS

5.1 Feasibility

Ninety-nine referrals were made to the trial – 97 from palliative care services (Inpatient: n = 88; community: n = 4; consult: n = 4; and research: n = 1), one from medical oncology, and one from psychiatry in sites without formal depression screening protocols (Figure 5.2). The referrals were primarily by physicians (n = 92) and nurses (n = 7). Within a period of ≤1 week from referral, 27 individuals proceeded to consent capacity assessment.

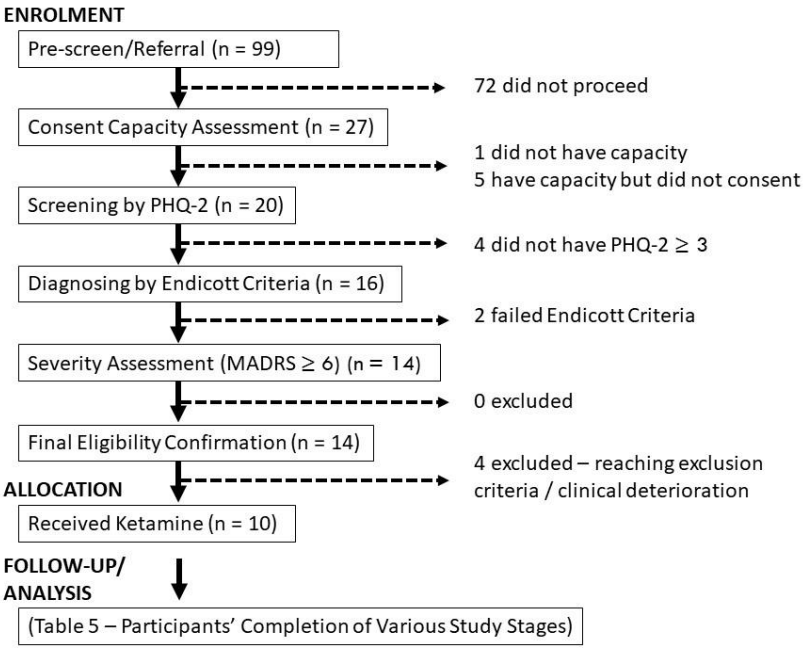


FIGURE 5. 2. CONSOLIDATED STANDARDS OF REPORTING TRIALS (CONSORT) FLOW DIAGRAM

Abbreviations: MADRS – Montgomery-Åsberg Depression Rating Scale; PHQ-2 – Patient Health Questionnaire-2

Reasons for referred individuals not proceeding to consent capacity assessment are shown in Table 5.3. They included (multiple reasons allowed for each individual referred): treating clinicians' decision to exclude potential participants from study on further assessments (n = 33, 41.8%) (e.g., due to the perceived lack of capacity to consent because of rapid clinical deterioration from underlying medical illnesses, and variations in depression assessment outcomes); meeting study exclusion criteria (n = 22; 27.8%); participant declining (n = 20; 25.3%) (e.g., not wanting medications as depression interventions, perceived study burden or competing priorities); and family declining (n = 4; 5.1%).

TABLE 5. 3. REASONS FOR REFERRALS NOT PROCEEDING FURTHER

	Number of Reasons (Aggregated Codes)[ʃ] for Initial Referrals not Proceeding Further (n = 79)	Prevalence (%) of Reasons/Codes Within (Sub)categories†
Treating Clinicians' Decision to Exclude from Study	33	41.8
Perceived lack of capacity to consent (including clinical deterioration from underlying medical illnesses)	18	54.5
Lack of significant depression objectively on assessment	10	30.3
Concerns of participant's anxiety	3	9.1
Concerns of participant's non-compliance	1	3.0
Clinician decision with reasons not specified	1	3.0
Exclusion Criteria	22	27.8
Antidepressant dose changes in the past 2 weeks	5	22.7
Recent substance misuse	5	22.7
Recent seizure	4	18.2
Liver function derangement	3	13.6
Glaucoma	2	9.1
Increase intracranial pressure	1	4.5
Hyperthyroidism	1	4.5
Poorly controlled hypertension	1	4.5
Participant Declining	20	25.3
Lack of significant depression subjectively	4	20.0
Declined but reason not specified	4	20.0
Desire for hastened death	3	15.0

Not wanting medications as depression intervention	3	15.0
Logistics	3	15.0
Competing priorities	2	10.0
Not wanting to talk about tragic past	1	5.0
Family Declining	4	5.1

[ʃ] Note: aggregated code n = 79 is higher than the 72 referrals that did not proceed to trial assessment because there could be multiple reasons/codes for this. For the purpose of calculating the prevalence values of reasons (or codes) for not proceeding, percentages were calculated based on the total aggregated code numbers, not the number of participants. The number of aggregated codes for each reason is the same as the number of participants giving that reason. †Prevalence values were calculated using the categories to which a code belongs as denominators.

Twenty-six individuals demonstrated having the capacity to consent, with 20 of those providing consent for the study and proceeding to screening for major depressive disorder using PHQ-2. Sixteen individuals screened positive for depression (PHQ-2 score ≥3). Fourteen people met Endicott Criteria for major depressive disorder and were assessed as having clinically significant severity (MADRS ≥ 16). Of the 14, three did not proceed due to meeting exclusion criteria (glaucoma, changes to antidepressant doses in the last two weeks, and a deranged liver function test). Eleven people had eligibility confirmed, but the health of one deteriorated substantially due to an underlying condition before ketamine commencement. Ten participants received ketamine and were analysed for responses: all ten had clinically significant depressive symptoms on referral; seven had pre-existing diagnoses of depression; and four met criteria for treatment-resistant depression (failing adequate trials of ≥ 2-lines of antidepressants as deemed by treating clinicians) (Table 5.4). Altogether there were 18 episodes of weekly ketamine administration, with the following dose concentrations and ranges: 0.1mg/kg (4-9mg) - n = 14; 0.2mg/kg (8-14mg) – n = 2; 0.3mg/kg (21mg) – n = 1; and 0.4mg/kg (28mg) - n = 1.

The accrual rate, adjusting for the months of trial closure due to COVID-19 related issues, was 0.54 participants per month across all sites. Attrition and completion rates of participants for each study stage are shown in Table 5.5, with eight participants reaching the end of week 1, four the end of week 4, and one the end of week 8 (study completion). Six participants were withdrawn from the study due to clinical deterioration from underlying illnesses, with two reaching withdrawal criteria based on study exclusion criteria. One died due to the underlying disease. Two participants self-withdrew due to the logistical burden. One person completed the study until the end of the follow-up.

TABLE 5. 4. DEMOGRAPHICS OF SKIPMDD PARTICIPANTS

	N / Median (Interquartile Range [IQR])
Number of participants	10
Gender (male)	7
English speaking	10
Primary palliative diagnoses	
Malignant disease	9
Haematological (myeloma, myelofibrosis)	2
Solid Tumour*	7
Gastrointestinal (including colorectal cancer)	3
Lung (Non-small cell lung cancer)	3
Breast	1
Prostate	1
Stage IV/Metastatic disease	7
Brain	2
Lung	4
Liver	3
Bone	5
Peritoneum	0
Non-malignant disease	1
COPD – severe	1
Clinical symptoms of depression	10
Pre-existing diagnosis of depression	7
History of treatment resistant depression (failing ≥ 2 lines of antidepressants)	4
Baseline	
AKPS	40 (20)
PHQ-2 score	5.0 (2.8)
Endicott Criteria score	7 (1.5)
MADRS score	32.0 (9.5)
BPRS score	39.5 (4.5)
CADSS score	1.5 (2.5)
Respiratory rate (/min)	18.0 (9.5)
Oxygen saturation (SaO2%)	97.0% (4.0)
Systolic blood pressure (mmHg)	99.0 (18.0)
Heart rate (/min)	97.5 (18.0)
Temperature (°C)	36.4 (0.5)

*Multiple-option item – i.e., including one participant with metastatic lung and breast cancers.

TABLE 5. 5. PARTICIPANTS' COMPLETION OF STUDY STAGES

Participant ID	Completion of data collection at the end of week (Week [number] Day 7)								Comments/Reasons for withdrawing from study
	1	2	3	4	5	6	7	8	
33/10/016									Clinical deterioration from underlying disease reaching an exclusion criterion (Tachycardia with fever deemed unlikely due to study intervention)
33/10/017									Clinical deterioration from underlying disease without reaching exclusion criteria (drowsy with possible delirium three days after completing ketamine infusion, deemed unlikely due to study intervention)
33/08/027									Participant died from disease progression of underlying metastatic lung cancer on the sixth day of the study
33/02/007									Condition deteriorated from underlying disease without reaching exclusion criteria (tachycardia on baseline assessment prior to receiving study intervention onset seven days after completion of ketamine infusion)
33/10/009									Logistical burden - no longer wished to be bothered (Self-withdrawn)
33/02/003									Clinical deterioration from underlying disease without reaching exclusion criteria (fatigue from disease progression and unable to engage in interview)
33/10/019									Clinical deterioration with occurrence of an exclusion criterion (atrial flutter prior to receiving the second dose of study intervention, deemed unlikely due to study intervention)
33/08/024									Logistical burden – "had enough" (Self-withdrawn)
33/08/013									Clinical deterioration from underlying disease without reaching exclusion criteria (frailty and severe hearing impairment, impairing study assessments)
33/08/019									"Very happy" for the trial processes involved but felt trial processes were at times burdensome when feeling unwell

Completion of study collection at end of the week (Week [number] Day 7)

Incompletion of study collection at the end of the week (Week [number] Day 7)

The primary reason for attrition was due to clinical deterioration from the underlying life-limiting illnesses and associated complications. No participants withdrew from the study due to unacceptable toxicity or intolerance of the intervention (as determined by the participant or site investigator). Participants reported finding the trial processes burdensome when feeling clinically unwell from the underlying terminal illness and its complications, contributing to the attrition rate. Frailty and functional decline posed logistical challenges for participants.

5.2 Safety & Tolerability

5.2.1 Psychotomimetic/Dissociative Effects

There was no clinically relevant increase in psychotomimetic (BPRS) or dissociative (CADSS) effects at any time point (0, 2hr, 4hr, 6hr) from baseline.

5.2.2 Heart Rate

One participant had a gradual increase in heart rate one hour after commencing the infusion at 0.3mg/kg and peaked with an increase over baseline of 51%, reaching 98 beats/min four hours after infusion completion. The participant attributed this to the questionnaire burden, although ketamine can increase irritability. The heart rate increase for that participant did not recur at the higher dose of 0.4mg/kg in the subsequent week. For the rest of the group, there was no clinically meaningful increase of median change from baseline heart rates at all time points on the intervention days (max +3.1%; +2.0 beats/min).

5.2.3 Blood Pressure

There was a dose-response increase in baseline systolic blood pressure with the highest increase of median change from baseline to be 7.9% (8.0mmHg), 12.8% (13.0mmHg) and 16.3% (16.0mmHg) for 0.1mg/kg, 0.2mg/kg and 0.3mg/kg doses respectively at the end of the ketamine infusion. The systolic blood pressure then normalised over the next four hours.

5.2.4 Other Adverse Events

For expected adverse events known to be associated with ketamine, apart from a mild increase in the prevalence of grade 2 somnolence (11% - 17%) and grade 1 headache (11% - 17%) for no longer than two hours of the infusion duration, no significant harms were encountered.

There were 86 reported adverse events in addition to the expected adverse events. Seventy-one events (82.6%) were deemed unrelated to the intervention, 12 events (14.0%) unlikely to be related, and three events (3.5%) possibly related (two were grade 1 hypertension with systolic blood pressures between 120 and 139, and one was borderline sinus bradycardia). None of these events was serious in nature. There was one serious adverse event for hospitalisation due to the underlying disease (imaging for possible spinal cord compression in the context of myeloma), deemed unrelated to the study intervention.

5.2.5 Antidepressant Effects

The total MADRS scores of individual participants over time are illustrated in Figure 5.3. Out of 18 episodes of ketamine administrations among the 10 participants, there were six occasions of positive responses (≥ 50% reduction in weekly baseline MADRS score) in five participants, all occurring after 0.1mg/kg infusions during week 1 (n = 4) and week 2 (n = 2). Three of the six occasions of positive responses occurred six hours after the infusion commencement (first dose – 0.1mg/kg: n = 2; second dose – 0.1mg/kg: n = 1), two on day 3 (both first dose - 0.1mg/kg) and one on day 7 (second dose – 0.1mg/kg). Only two participants received dosages ≥ 0.2mg/kg with mixed responses: one participant achieved a positive response and remission at the highest dosage of 0.2mg/kg; and another did not achieve a positive response despite dose escalation to 0.4mg/kg.

For the prevalence of positive response (≥ 50% reduction in individuals' baseline MADRS score from study commencement) by participants over the study course, using the total MADRS score, five out of 10 participants (50%) had positive responses during the week of having received ketamine infusion, with two participants having sustained positive response on day 7 after the infusion. All five positive responses occurred with the 0.1mg/kg dosing. As clinical deterioration from underlying life-limiting illnesses can mimic somatic items of major depressive disorder, on excluding the somatic MADRS items, there were more participants with positive responses (six of ten). Three of the six participants who developed positive responses during the week had sustained positive responses on day 7 post-infusion. For suicidal ideation (MADRS item 10), nine of 10 participants had a ≥ 50% reduction in baseline suicidal ideation during the intervention week. Seven of these nine participants sustained a ≥ 50% reduction in baseline suicidal ideation on day 7 post-infusion.

Three participants achieved remission during the study. Out of these, two relapsed within seven days of remission.

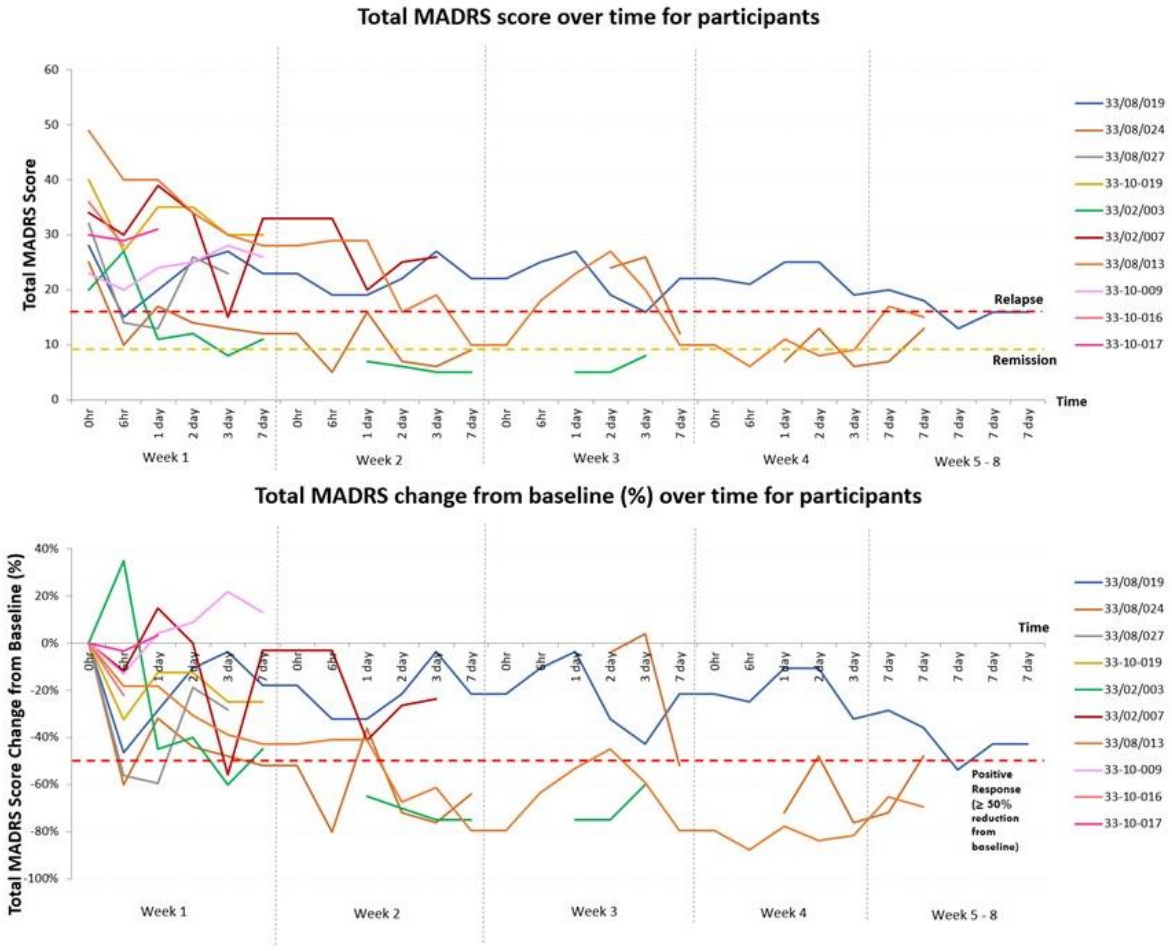


FIGURE 5. 3. TOTAL MADRS SCORE CHANGES OVER TIME FOR PARTICIPANTS

Abbreviation: MADRS - Montgomery-Asberg Depression Rating Scale.

5.2.6 MADRS & Pain Correlation

There were no statistically significant associations between total MADRS (Kendall's tau ranging from -0.13 to -0.49) and MADRS scores without somatic items (Kendall's tau ranging from -0.06 to -0.55) with NPRS pain score.

5.2.7 Quality of Life

Of the total of 64 episodes of Q-LES-Q-SF questionnaire attempts, only four (6.3%) were completed. While the single item of "overall life satisfaction" was completed in 48 out of 64 (75%) episodes, none of the participants sufficiently

completed Q-LES-Q-SF longitudinally throughout the study duration to allow meaningful pre- and post-intervention comparison.

5.2.8 SKIPMDD Participant Questionnaire

No participant completed the participant satisfaction questionnaire at study withdrawal or completion, due to deteriorating medical conditions and questionnaire burden.

6. DISCUSSION

6.1 Key Findings

On the basis of the recruitment rate and the positive response rate set *a priori*, a definitive ketamine trial for major depressive disorder in the palliative care setting involving people with extremely short prognoses of days to weeks may be feasible. Key feasibility barriers identified related to: trial closures due to COVID-19 pandemic; clinicians' challenges of screening and assessing for depression in the palliative care setting (corroborate Chapter 4's findings); participants' rapidly deteriorating medical conditions; and personal preferences and perceptions (e.g., the perceived study burden and the wish to avoid medications). Individual dose-titration of subcutaneous infusions of ultra-low ketamine dosages starting from 0.1mg/kg over two hours can be well-tolerated, and produce transient but notable improvements for major depressive disorder symptoms over hours to days.

6.2 Feasibility barriers

Palliative care clinicians at the participating sites lacked training in screening, assessing, and managing depression. Despite the prevalence of deprssion, there was no routine screening in the palliative care context.[305] Consistent with the literature, palliative care clinicians were hesitant to diagnose major depressive disorder, feeling unsure of their assessment.[297] On deferring the diagnosis to the psychiatry team, the investigators found that there was often a lack of timely access to psychiatry services at the local sites, while participants' rates of clinical deterioration were rapid. This corroborate other studies' finding that there is a general lack of timely access of mental health services among palliative care services, as elaborated in the previous mixed-methods study in

Chapter 4.[67, 69, 297, 362] Ideally, psychiatric assessment in this clinical situation should be performed within 24 hours to allow timely interventions. Apart from increasing service resources, improving linkages between existing palliative care and psychiatry services at local sites (e.g., establishing regular integrated palliative care psychiatry MDT meetings) is pivotal for optimising the feasibility of a future definitive trial, minimising the lag time between participants consenting to the study and receiving the study intervention.[362] It may also yield better consistency between palliative physicians' and psychiatrists' approaches to screening, assessing and managing major depressive disorder in the palliative care context, while improving the relevant knowledge base for clinicians from both disciplines.[297, 362]

Like many palliative care trials, the primary reason for attrition identified in this study was the clinical deterioration of participants due to their underlying terminal illnesses and associated complications. As such, any trial involving people with major depressive disorder and advanced life-limiting illnesses must be designed to minimise the study duration. The trial design must allow for the timely administration of study interventions with rapid dose-escalation and close monitoring for toxicity using low-burden tools as infrequently as possible. For example, the study duration may be compressed to two to four weeks. Instead of using the conventional BPRS and CADSS for psychiatric adverse events, the Ketamine Side Effect Tool can be considered to lower the questionnaire burden.[403] Even Q-LES-Q-SF, chosen for its comprehensive psychosocial domain assessment and brevity compared to other common oncological quality-of-life tools (e.g., EORTC QLQ-C30),[404] seemed too burdensome for participants; alternatives need to be explored.

6.3 Tolerability & Antidepressant Activities

Unlike the ketamine burst protocol for cancer pain (100-500mg/day), which participants found difficult to tolerate,[134] this study shows that ultra-low dosages of ketamine for depression starting at 0.1mg/kg over two hours are safe and well-tolerated. Additionally, this study demonstrated rapid-onset (even four hours after infusion) antidepressant activities at dosages less than the conventional psychiatric dosing of 0.5mg/kg given subcutaneously.[138, 230] The

effect size was promising, with a 50% positive response rate during the week of intervention using total MADRS scores, and higher if excluding somatic symptoms due to underlying medical conditions. Antidepressant activity appeared to be short-lived (hours to days). Due to the high attrition rate and the transient beneficial effect at these ultra-low dosages, future studies should consider shorter periods between re-dosing (e.g., twice weekly dosing).

Ketamine is known for its potential analgesic properties. The current study measured the correlation between the antidepressant response of ketamine and the analgesia effect perceived by participants, finding it to be insignificant. However, due to the small sample size and the likely resultant high variability observed in the correlation coefficients, the study was unable to reliably ascertain this finding.[405]

6.4 Capacity to Consent

In concordance with the literature, this study provides evidence that treating clinicians might act as gatekeepers, deterring potential participants in clinical research.[65] This might relate to their perceptions of how unwell the potential participants were, assuming their lack of capacity to consent, and that participation may cause undue burden to these individuals without meaningful benefits.[65] Interestingly, most potential participants who were allowed to proceed to consent capacity assessment retained the capacity to consent, despite their high degree of frailty. Furthermore, while the study assessment tools were found to be burdensome, the actual intervention was well tolerated and produced timely but transient antidepressant activities for most participants, especially in reducing suicidal ideation and the desire for death. Within the limitation that these participants might have already been filtered by the treating clinicians to retain capacity to consent, future clinicians might consider lowering their gatekeeping threshold for palliative patients to participate in research, allowing them to have formal capacity assessment as part of the trial assessment.[65] This may maximise the individual's chance of receiving potentially meaningful benefits from trial participation.[65]

6.5 Implications

This study raised several implications at the clinician, health system, policy and research levels. The role of ketamine in the symptomatic treatment of major depressive disorder warrants exploration in future definitive studies, especially in the presence of suicidal ideation when prognoses are too short for typical interventions to work. Depression screening and assessment using ultra-short questionnaires (e.g., PHQ-2) and Endicott Criteria, respectively, seem feasible for major depressive disorder in the palliative care setting.[78, 81]

For research, to improve the feasibility of a definitive trial, not only should the identified barriers be addressed, but consideration should be given to non-conventional study designs, such as the aggregated n-of-1 design or Bayesian response adaptive randomisation.[233, 236, 332] Importantly, future studies need a careful balance between narrowing eligibility criteria to maximise detectable treatment response (e.g., only including non-treatment resistant depression) and broadening the eligibility to enhance recruitment with the risk of diluting the effect size. The prognostication eligibility criterion could also be considered using the absolute cut-off of AKPS ≤ 40, a relative change of AKPS, or following participants until death. Adequately powered studies can examine differences in response according to treatment resistance status, first versus subsequent dosing, and subjective versus objective depressive items. The collection of brief but regular qualitative data throughout the study course from both participants and carers may help capture objective treatment responses (e.g., social engagement). Lastly, while possibly less efficacious than parenteral ketamine, ketamine and esketamine nasal spray may be alternatives in future studies to enhance study feasibility.[320, 360, 406]

6.6 Strengths and Limitations

To the authors' knowledge, this study is the first prospective study providing key feasibility, safety, tolerability and potential antidepressant activity data for future definitive trial design exploring subcutaneous ketamine for major depressive disorder at dosages lower than the conventional psychiatric dose of 0.5mg/kg in a population with extremely short prognoses. It recruited despite multiple trial closures due to COVID-19. It included generous study eligibility criteria to allow

for improved generalisability towards the palliative care population with significant co-morbidities and frailty. The individualised dose-titration study design minimised drug toxicity to participants. The monitoring of toxicity using standardised measures in psychiatry (i.e., BPRS and CADSS) and palliative care research (NCI CTCAE) allowed meaningful comparison of this study with the relevant literature.

There were several limitations of the study for this study. Due to ethical and feasibility concerns, the study was designed as an open-label single-arm design without a placebo or an active comparator arm. This could inflate the true effect size of ketamine through potential assessor bias, Hawthorne effect, and regression to the mean.[407-409] With its primary objective focusing on feasibility, this study was not intended to be powered for inferential statistics, determining the effectiveness of study intervention against the standard-of-care, nor for subgroup analyses to differentiate treatment effects between different dosages of ketamine, first versus subsequent dosing and treatment-resistant status. Building on this feasibility study, future adequately powered studies are needed. There were intrinsic limitations in the assessment of major depressive disorder in advanced life-limiting illnesses. Even though Endicott Criteria have been used to reduce the over-identification of cases of major depressive disorder, they have not been extensively validated in the palliative care setting, highlighting the need for future research in this field.[15, 373]

7. CONCLUSION

A future definitive trial of the use of subcutaneous infusion of ketamine for major depressive disorder in the palliative care setting may be feasible, but faces barriers related to clinicians' challenges in screening and assessing for depression in this setting, participants' rapidly deteriorating medical conditions, and personal preferences and perceptions. Individual dose-titration of subcutaneous infusions of ultra-low ketamine dosages, starting at 0.1mg/kg over two hours, can be well-tolerated and produce transient antidepressant effects over hours to days.

CHAPTER 6: INTEGRATION OF THESIS FINDINGS & CONCLUSION

1. SYNTHESIS OF FINDINGS

The research presented in this thesis explored the complexities of depression care in people with advanced life-limiting illnesses and extremely short prognoses of days to weeks of life. The Tansella and Thornicroft's framework (Chapter 1, Section 3.1) was used to delineate the complex and multi-level interactions between aspects of caring for depression in people with advanced life-limiting illnesses who have extremely short prognoses.[163] The nine-cell matrix, created from three variables in both the geographical (country, local, and patient) and temporal dimensions (inputs, processes, and outcomes), was designed to help relevant stakeholders solve complex issues relating to mental health service reform. The findings from two systematic reviews, a mixed-methods study, and a phase II feasibility study of a pharmacological intervention within this doctoral program have provided some answers for the knowledge gaps identified through the Tansella and Thornicroft's matrix in Chapter 1 (Table 6.1), enabling optimisation of care for affected individuals.

TABLE 6. 1. MODIFIED TANSELLA AND THORNICROFT'S MATRIX SYNTHESISING FINDINGS OF CURRENT DOCTORAL PROGRAM - DEPRESSION CARE IN PEOPLE WITH ADVANCED LIFE LIMITING ILLNESS AND EXTREMELY SHORT PROGNOSES

Geographical Dimension	Temporal Phase		
	(A) Input	(B) Process	(C) Outcome
(1) International Literature **(Systematic Reviews)**	-50% of this population has clinically significant depressive symptoms, with up to half being first episode depression -There is no randomised controlled trial evidence for any interventions (non-pharmacological or pharmacological) in this population.	-Depression assessment methods used in this setting vary, but include depression-specific tools (HADS, PHQ-8/9, DRS) and DSM/ICD diagnostic criteria. -Depression prevalence measured by HADS might reflect the combined prevalence of various depressive disorders using diagnostic criteria - Interventions with rapid-onset antidepressant properties from the general palliative care literature warrants further research in the extremely short prognosis setting (i.e. life review, dignity therapy, ketamine, methylphenidate and psilocybin)	-Depression screening, assessment and early intervention prior to progression of life-limiting illnesses towards extremely short prognosis setting are necessary -Responses (benefits and harms) of any interventions for depression (non-pharmacological and pharmacological) should be diligently monitored as in experimental trials in this setting
(2) Local – Australasian context **(Mixed-methods study of palliative**	Clinician perceptions of: -Inadequacy of clinician training in necessary palliative care psychiatry skills among palliative physicians and psychiatrists	-Lack of routine depression screening -Inter- and intra-disciplinary variations in depression care approaches -Uncertainty when assessing depression aetiology	Postulated improvement strategies centred around integrated care processes between palliative care and psychiatry services to:

physicians and psychiatrists)	-Poor access to necessary interventions -Suboptimal linkages between palliative care and psychiatry -Lack of research support -Society stigma and unsupportive attitudes	-Less likely to appropriately intervene for depression in this setting than in the better prognosis setting (not intervening or inappropriately using pharmacological interventions)	-Improve clinician training (e.g., joint education presentation or trainee rotations) -Establish supportive health systems (e.g., integrated multidisciplinary team meetings or ward rounds) -Promote integrative research with inclusive but innovative research designs (e.g., n-of-1 or pre-consent)
(3) Patient **(Phase II pilot feasibility study)**	- Ongoing effort to reduce study burden (e.g., questionnaire burden, long study duration, and interventional harms) to enhance compliance and tolerability is needed due to rapidly deteriorating medical conditions of participants	-For major depressive disorder in the setting of advanced life-limiting illnesses and extremely short prognoses, the following can be feasible: --Screening using PHQ-2, an ultra-short item questionnaire --Diagnosis using Endicott Criteria, a substitutive approach to the standard DSM diagnostic criteria. -Identified feasibility barriers for future definitive trials corroborate with issues identified in the survey and focus group studies:	Individual tailored dose-titration of subcutaneous infusions of ultra-low ketamine dosages starting from 0.1mg/kg over two hours (in contrast to the conventional 0.5mg/kg dosing in the psychiatry literature) can be: -Well-tolerated in the extremely short prognosis setting -Produce transient but notable improvements in major depressive disorder symptoms over hours to days

		--Clinicians' challenges of depression screening and assessment in the palliative care setting --Participants' rapidly deteriorating medical conditions require modifications to study design and procedures --Preferences (e.g., the wish to avoid medications) and perceptions (e.g., perceived burden of research participation) of participants, family and clinicians require ongoing cultural change. -Postulated strategies centred around integrative care processes between psychiatry and palliative care services might improve the feasibility of a future definitive study	

Abbreviations: DRS – Depression Rating Scale; DSM –_Diagnostic and Statistical Manual of Mental Disorder; HADS – Hospital Anxiety and Depression Scale; ICD - International Classification of Diseases and Related Health Problems; PHQ – Patient Health Questionnaire

At the international literature level, through the first systematic literature review, a high prevalence (50%) of clinically significant depressive symptoms among people with advanced life-limiting illnesses and extremely short prognoses has been identified (1A). This is higher than that of the general palliative care population. This review also identified the various methods of assessing clinically significant depressive symptoms in people with extremely short prognoses (1B). Importantly, these symptoms might not be diagnosed as the commonly known depressive disorders (e.g., major depressive disorders) via the DSM and ICD diagnostic criteria due to the diagnostic challenges related to terminal illnesses. Instead, they may be identified as clinically significant by reaching thresholds set by various depression-specific tools (e.g., HADS, PHQ-8/9, and DRS) validated in the general palliative care setting, therefore necessitating interventions (1A).

This systematic review raises the possibility that palliative physicians who are not trained in conducting psychiatric interviews to diagnosis various depressive disorders using the standard DSM and ICD diagnostic criteria can consider identifying clinically significant depressive symptoms using these tools in the extremely short prognosis setting. It also suggests that depression-specific tools such as HADS might measure the combined prevalence of various depressive disorders diagnosed by diagnostic criteria (1B). Therefore, clinicians and researchers must carefully consider what they are measuring when assessing clinically significant depressive symptoms and interpret their findings according to their chosen assessment methods (i.e., the depression-specific tools or certain diagnostic criteria) (1B).

While clinically significant depressive symptoms are prevalent, the systematic review of potentially effective interventions (Chapter 3) identified a lack of RCT evidence to support any non-pharmacological and pharmacological interventions for these symptoms when prognoses are extremely short (1A). It is essential, therefore, for clinicians and researchers to realise that all interventions for depression are still experimental in nature for these individuals, being based on data extrapolated from other populations and settings. The outcomes of depression interventions for people with better prognoses may not

be generalisable to people with extremely short prognoses (1C). This evidence gap highlights the need for innovative research designs for depression in palliative care settings that are feasible and inclusive of people with extremely short prognoses.

Importantly, the first systematic review (Chapter 2) provided evidence that up to half of people with clinically significant depressive symptoms and extremely short prognoses experience these symptoms as their first episode of depression without previously known depressive disorders.[180, 181] Further studies are needed to explore the potential contributors, which might include: the progressive pathological processes of life-limiting illnesses (e.g., hypercalcaemia); associated symptom distresses; functional limitations; grief; hopelessness; loss of dignity; relational concerns; and existential distress.[305] Meanwhile, processes need to mitigate the effects of these potential contributors and lower the incidence of first episode depression at the end of life. Routine, feasible and effective screening and diagnostic processes must be established at local health service level, along with infrastructure that facilitates rapid mental health interventions for these symptoms when patients' prognoses are relatively long, as highlighted by the mixed-methods study (Chapter 4) (1C).

From the local Australasian context, the mixed-methods study described in this thesis was the first to describe the approaches and perspectives of palliative physicians and psychiatrists towards depression care in people with advanced life-limiting illnesses and extremely short prognoses. These clinicians perceived caring for depression in people with extremely short prognoses to be complex and challenging. There was a sense of nihilism expressed, contributed by: the perceived inadequacy of clinician training in necessary palliative care psychiatry skills; the lack of supportive health infrastructure (poor access to necessary interventions and suboptimal linkage between palliative care and psychiatry); the lack of research support; and societal stigma and unsupportive attitudes (2A/2B). Unsurprisingly, the Australasian palliative physicians and psychiatrists studied herein reported suboptimal depression care delivery.

Overall, the survey data showed a lack of depression screening, inter- and intra-disciplinary variations in care approaches, and uncertainty about assessing

depression aetiology. Clinicians reported a reduced likelihood of appropriately intervening for depression when prognoses are extremely short as compared to when prognoses are better (e.g., using foundational non-pharmacological interventions and adding adjunct pharmacological interventions as indicated) (2B). Despite the first systematic review identifying the availabilities of various depression screening tools for use in palliative care, reasons underlying the lack of depression screening with a poor uptake of their use are worth exploration. The subsequent qualitative focus group study provided some insight into the potential reasons. Palliative physicians reported concerns about the screening tools' feasibility and burden for unwell and fatigued patients, especially tools containing many questionnaire items. Additionally, palliative physicians may have not been trained to use these screening tools effectively, fearing that they might disrupt the therapeutic relationship with the patients by administrating them in a checklist manner. Many were unaware of the low-burden screening tools such as the ultra-short one-to-two-item questionnaires. In contrast, while psychiatrists were perceived to be experienced in depression screening and assessment, it was reported that many psychiatrists had not received training to deal with individuals at the end-of-life, and lacked the resources to deliver the care. The studies highlighted the urgent need for better psychiatry-palliative care service integration to facilitate better palliative care and psychiatry clinician training and timely patient access to necessary interventions.

The sequential quantitative survey and qualitative focus group study further clarified the training needs for palliative physicians and psychiatrists, informing the required training contents as perceived by these clinicians. Furthermore, as the participants identified, not only the medical professionals need training, but the relevant nurses, allied health staff and even community volunteers. This study established that the training contents should include the safe and effective use of screening, assessment, and management strategies, delivered to patients in a low-burden manner. For example, clinicians need to learn how to effectively utilise appropriate tools and diagnostic criteria to screen and assess for depressive symptoms while maintaining patient rapport. They need to be able to differentiate normal versus pathological depression, and the effects of terminal illnesses from the somatic symptoms of depression. Clinicians need to

learn to consider and differentiate between important differential diagnoses (e.g., hypoactive delirium). For management, the high prevalence of depressive symptoms in people with extremely short prognoses and individuals' hope for clinician competency in discussing psychological distress support training all clinicians working in this field with the skills of foundational non-pharmacological interventions (e.g., the communication approach of attentive listening with empathy used in supportive psychotherapy).[305, 317] This may minimise inappropriate prescribing of pharmacological interventions. Palliative care clinicians need to be trained in when and how to escalate care, including when to consider pharmacological options and referral to specialist psychiatry services. They also need to know how to liaise with regulatory bodies to access restricted interventions (e.g., methylphenidate), administer interventions in ways that minimise harm while maximising benefits, and appropriately engage with dying patients for research and trial interventions. Meanwhile, research should be conducted to explore methods of delivering non-pharmacological and pharmacological interventions, in ways that optimise tolerability and effectiveness for affected individuals.

Clinician participants suggested strategies of integrating palliative care-psychiatry service care processes to enhance care for depression in people with advanced life-limiting illnesses and extremely short prognoses. Specific strategies were devised to target improving clinician training (e.g., joint education presentation or trainee rotations), establishing supportive health systems (e.g., integrated MDT meetings or ward rounds), and promoting integrative research with inclusive but innovative research designs (e.g., n-of-1 or pre-consent) (2C). The effectiveness of these strategies in improving patient outcomes for people with clinically significant depressive symptoms and extremely short prognoses is currently unknown and warrants more research.

At the patient level, as identified in the systematic review in Chapter 2, there is a sub-group of patients with clinically significant depressive symptoms suffering from major depressive disorder that may require additional pharmacological interventions in addition to the foundational non-pharmacological interventions to receive timely and meaningful benefits. Given the short timeframe for

interventions to benefit people with extremely short prognoses, there is a need for a rapid-onset antidepressant that can be administered reliably and tolerated well, despite co-existing symptom burden (e.g., dysphagia, fatigue, and organ dysfunctions). The systematic review finding of the lack of RCT evidence in this field (Chapter 3) imply that existing effective treatments for depression in the other fields cannot be generalised to people with extremely short prognoses. Furthermore, research to determine the effectiveness of pharmacological interventions in this frail and often very ill population is often hindered by a multitude of feasibility concerns, as identified in the mixed-methods study.[63, 297, 361, 362] The feasibility of trial designs and procedures need to be explored to ensure meaningful outcomes from future definitive trials.

Ketamine is an emerging intervention against major depressive disorder in the psychiatry population without advanced life-limiting illnesses with rapidly evolving evidence base (Chapter 5 Section 2.3).[138, 139, 144, 353, 410] It has rapid-onset antidepressant effects, even against treatment resistant depression.[138, 139, 354] However, its effectiveness is of short duration (range of days); medium-term and longer-term benefits are uncertain.[353, 354, 410] Despite ketamine's high relapse rate, its strong and rapid-onset antidepressant effect make it a potentially useful antidepressant in the palliative care population with extremely short life expectancy.

Nonetheless, in this population with extremely short prognoses, which ketamine dosages were tolerable and whether they could produce the desired antidepressant signal in the context of progressive advanced life-limiting illnesses remains uncertain. While a phase III study is necessary to answer this question, the feasibility of running such a study in this extremely short prognosis setting is questionable. Therefore, a phase II feasibility study (SKIPMDD) was conducted to explore the feasibility, safety, tolerability, acceptability, and antidepressant signal of ultra-low dosages of ketamine given with an individually tailored dose titration approach via subcutaneous infusion for major depressive disorder in the setting of extremely short prognosis.

The SKIPMDD study described in Chapter 5 showed that a definitive ketamine trial for major depressive disorder among people with prognoses of days to

weeks of life may be feasible, as indicated by the recruitment rate and the positive antidepressant response rate set *a priori*. It found that the rapidly deteriorating medical conditions, the associated complications, and the poor functional status necessitate ongoing efforts from researchers to reduce study assessment burden and compress study procedures into the shortest possible timeframe (3A). Rapid-response trial processes, such as those from the critical care setting (e.g., embedding study procedures into routine care) may help optimise potential participants' opportunities for trial participation and minimise attrition rate.[411]

As informed by the focus group participants, SKIPMDD identified that the primary reason (23%; 18 out of 79) for referrals to the trial not proceeding further to be the treating clinicians' perception of individuals lacking ability to consent due to clinical deterioration from their underlying illnesses. This correlates with the systematic review finding of a lack of inclusion of people with extremely short prognoses in clinical trials (Chapter 3) and the focus group findings of clinicians' perceptions of participants' low tolerance of research processes (Chapter 4). This provides further evidence that clinicians and researchers in this field may be acting as gatekeepers for these affected individuals, seeking to prevent harm.[65] Importantly, SKIPMDD demonstrated that despite the participants being significantly depressed and ill at baseline (e.g., mostly bedbound with borderline tachycardia and significant co-existing symptom burden), most retained the capacity to consent to participate in research and were willing to do so. Like other vulnerable populations (e.g., older people with cognitive impairment), it is imperative that clinicians do not withhold opportunities for research participation out of the intention to do no harm, but to consider supportive strategies should their patients desire to participate.[228]

The SKIPMDD study identified feasibility barriers that must be overcome before a definitive study can be conducted. These barriers are related to: clinicians' challenges of screening and assessing for depression in the palliative care setting; the high attrition rate from participants' rapidly deteriorating medical conditions; and personal preferences and perceptions (e.g., the perceived study burden and the wish to avoid medications) (3B). These barriers reflect the

findings from the survey and focus group studies, highlight the need for clinician training, and encourage further implementation studies exploring the effectiveness of postulated strategies of integrated care processes between psychiatry and palliative care to improve overall care and research in this setting. Importantly, the SKIPMDD study provided evidence that screening for major depressive disorder using low-burden ultra-short questionnaires (e.g., PHQ-2) and diagnosing such in the context of co-existing terminal illnesses using a substitutive approach of Endicott Criteria may be feasible, as suggested in the focus groups, supporting training clinicians with their use (3B).

Informed by the previous studies of the doctoral program, there is a need to find a rapidly effective intervention for major depressive symptoms in this space of advanced life-limiting illnesses and extremely short prognoses, when the affected individuals might be too physically and mentally unwell to effectively engage with psychotherapies to obtain full benefits. The SKIPMDD study has extended the current knowledge about ketamine use for major depressive disorder. Rather than the conventional intravenous infusion at 0.5mg/kg over 40 minutes, which has tolerability concerns for the extremely short prognosis sub-group according to the cancer pain literature, this study provided evidence that individually tailored dose-titrations of subcutaneous infusions of ultra-low ketamine dosages starting from 0.1mg/kg over two hours can be well-tolerated.[134] Furthermore, adding to Loo et al.'s (2016)[230] finding of efficacy of ultra-low dose subcutaneous ketamine boluses, SKIPMDD found that ketamine subcutaneous infusion at these dosages produces a transient but notable rapid-onset antidepressant signal against major depressive disorder over hours to days in this medically unwell population (3C). This study, therefore, represents a foundation for building the future definitive study investigating the effectiveness of ketamine in people with major depressive disorder and extremely short prognoses.

Though this doctoral program was unable to definitively identify an intervention that is effective in this extremely short prognosis population, it tackled some key methodological problems and produced a better understanding of the clinical context in which depression is treated, facilitating further exploration of effective

therapies. The data presented herein support the need for early intervention before prognoses become extremely short, using various psychotherapies delivered in a supportive nature via the multi-disciplinary palliative care team with intimate psychiatry service integration. Adjunct typical antidepressants and rapid-onset pharmacological agents should be considered early, and administered in an experimental manner with diligent monitoring of harms and benefits until further evidence is generated.

2. ETHICAL CONSIDERATIONS

This doctoral program did not include an in-depth exploration of the ethical issues of caring for depression in the extremely short prognosis setting. Nonetheless, it generated some findings on which future studies can build to explore the ethics inherent to this topic.

Firstly, the high prevalence of clinically significant depressive symptoms found in the first systematic review justifies the prioritisation of health resources to address this issue. This, coupled with the sense of therapeutic nihilism, the perceived inadequacy in palliative care psychiatry skills, and the lack of required resources identified by clinicians in the mixed-methods study, provides an even stronger argument for prioritisation. One might argue, from the notion of non-maleficence towards patients and staffs, that health professionals should not be placed in the position of providing care to patients when they do not feel adequately trained or empowered to do so. Initiatives to better equip clinicians working in this field to minimise the potential harm and distress to clinicians and individuals with depression at the end of life are urgently needed.

The systematic review finding of the lack of RCT data to inform effective depression interventions in this setting suggests that clinicians should carefully consider low-burden clinical trials of potentially helpful interventions as a form of depression treatment to maximise beneficence for the affected individuals while monitoring for potential harm. The data from the mixed-methods study suggest that clinical trial study designs in this field should be feasible, low-burden, innovative and flexible to support the changing needs and high symptom burden of the participants.[65] Efforts to facilitate working relationships between the research teams, palliative care and psychiatry clinical teams and these affected

individuals need to be considered to overcome the practical and ethical challenges of running trials in this population.[65] With an empathetic approach, the autonomy of these vulnerable individuals should still be advocated through supportive strategies that facilitate inclusivity while diligently monitoring for harm and changes in consent, avoiding inappropriate “gate-keeping” and clinician paternalism.[65]

The results of the SKIPMDD feasibility study attest that individuals with major depressive disorder and extremely short prognoses may still have the capacity to consent and receive benefits from research participation. Future researchers should consider exploring methods of consent processes that can support the autonomous decisions of these vulnerable individuals should they wish to participate, and continuously and sensitively monitor for changes in attitude toward trial participation.[65] The high attrition rate and the poor functional status of the participants affirm the recommendation of the focus group participants that trials must be conducted in innovative ways that are adaptive to the needs of these individuals.[65]

3. LIMITATIONS OF THE DOCTORAL PROGRAM

Specific limitations relating to individual studies are discussed in previous chapters. This section highlights some general limitations of this doctoral program, for the benefit of future researchers.

A key limitation of this doctoral program was that this doctoral program is established on the assumption that clinicians can identify and differentiate people with extremely short prognoses from people earlier in the disease trajectory. However, as discussed in Chapter 1 Section 1.3, prognostication can be difficult. Future researchers in this field will need to consider the effects of different methods of prognostication and assess survival on the measured study outcomes for depression in palliative care research.

The perspectives of people with advanced life-limiting illnesses and extremely short prognoses could not be explored exhaustively in this doctoral program. Even in the clinical trial (SKIPMDD), the exploration was limited by the participants’ disease progression and co-existing symptom burden.

Furthermore, the candidate and his colleagues did not study the perspectives of these affected people's family members and non-professional carers. Adding concurrent qualitative sub-studies to the definitive trial to explore these areas would be helpful, especially as the trial identified that the objective signs of depressive symptoms may improve sooner than the subjective depressed mood change. For example, participants' psychomotor retardation and social interactions might improve and be noticed by carers and family members before participants experience subjective mood improvement. Given that a goal of depression treatment is to improve conversations between affected people and their important persons, capturing these persons' perspectives may be invaluable.

While the perspectives of palliative physicians and CL psychiatrists were explored, the viewpoints of other health professionals of the multi-disciplinary team who provide care for these affected individuals (e.g., palliative care nurses, social workers and pastoral care workers) were not studied. The Australasian context of the survey and focus group studies may also reduce the generalisability of the study's findings. Future studies should consider studying the perspectives of these clinicians and include participants from other countries. Furthermore, in the limited timeframe and resourcing of this doctoral program, a Delphi study to help reach consensus between palliative physicians and psychiatrists on depression care approaches in the extremely short prognosis setting could not be performed.

Regarding interventions for depression, the findings of this doctoral program have been predominantly centred around pharmacological approaches with a lack of coverage of non-pharmacological interventions. The program intended to explore potentially effective interventions, including non-pharmacological interventions, in the international literature through systematic reviews of randomised controlled trial data. It was planned to culminate in the investigation of the feasibility of a rapid-onset pharmacological agent in the "worst case scenario" (severe or treatment-resistant depression requiring pharmacological interventions when prognoses are short). Future research, especially clinical trials, should investigate non-pharmacological interventions in this short

prognosis setting. Importantly, researchers should explore which non-pharmacological intervention can be feasible, tolerable, effective, and become the foundational depression intervention for pharmacological interventions to build on if needed for people with depression and extremely short prognoses.

Given the lack of randomised controlled trials in this area and the challenges in conducting such in the extremely short prognosis setting, evidence generated from high-quality non-randomised controlled trials must also be considered in future systematic literature reviews. Despite not finding the RCT evidence to support any depression intervention in the extremely short prognosis setting, our systematic review identified some rapid-onset non-pharmacological (life review and dignity therapy) and pharmacological interventions (e.g., ketamine, methylphenidate, psilocybin). Future studies should consider exploring these other potentially rapid-onset depression interventions identified, as they might be potentially helpful for our target population.

Finally, the doctoral program did not explore the health economics of care in the target population. Future studies of strategies to improve psychiatry and palliative care service integration and interventions for depression should consider the economic costs and benefits of such initiatives.

4. CONCLUSION

This doctoral program explored the issue of depression in people with advanced life-limiting illnesses and extremely short prognoses with life expectancy in the range of days to weeks. It established that a high prevalence of depression exists in this population, and confirmed the lack of high-quality evidence for any effective intervention in this setting. It highlighted the complexity of caring for depression in the palliative care setting from the perspectives of palliative physicians and psychiatrists, identifying an urgent need for better clinician training, research, service linkage, and cultural change through the integration of care processes between palliative care and psychiatry services. It also provided key feasibility data for conducting a future definitive study of ketamine as an antidepressant in this context, establishing its safety, tolerability and rapid onset but transient anti-depressant signal when given as a subcutaneous

infusion through individually tailored dose titration. Together, these study findings serve as the cornerstone for driving processes that optimise depression care in the extremely short prognosis setting for clinicians, health service and policy developers, and researchers.

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APPENDICES

Appendix 1. Prevalence Systematic Review Paper (Journal of Pain and Symptom Management)

Review Article

Clinically Significant Depressive Symptoms Are Prevalent in People With Extremely Short Prognoses—A Systematic Review

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Abstract

Context. Currently, systematic evidence of the prevalence of clinically significant depressive symptoms in people with extremely short prognoses is not available to inform its global burden, assessment, and management.

Objectives. To determine the prevalence of clinically significant depressive symptoms in people with advanced life-limiting illnesses and extremely short prognoses (range of days to weeks).

Methods. A systematic review and meta-analysis (random-effects model) were performed (PROSPERO: CRD42019125119). MEDLINE, Embase, PsycINFO, CINAHL, and CareSearch were searched for studies (1994–2019). Data were screened for the prevalence of clinically significant depressive symptoms (assessed using validated depression-specific screening tools or diagnostic criteria) of adults with advanced life-limiting illnesses and extremely short prognoses (defined by survival or functional status). Quality assessment was performed using the Joanna Briggs Institute Systematic Reviews Checklist for Prevalence Studies for individual studies and Grading of Recommendations Assessment, Development and Evaluation (GRADE) across studies.

Results. Thirteen studies were included. The overall pooled prevalence of clinically significant depressive symptoms in adults with extremely short prognoses ($n = 10$ studies; extremely short prognoses: $N = 905$) using depression-specific screening tools was 50% (95% CI: 29%–70%; $I^2 = 97.6\%$). Prevalence of major and minor depression was 10% (95% CI: 4%–16%) and 5% (95% CI: 2%–8%), respectively. Major limitations included high heterogeneity, selection bias, and small sample sizes in individual studies.

Conclusions. Clinically, significant depressive symptoms were prevalent in people with advanced life-limiting illnesses and extremely short prognoses. Clinicians need to be proactive in the recognition and assessment of these symptoms to allow for timely intervention. J Pain Symptom Manage 2021;61:143–166. © *2020 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words

Palliative Care, Prognoses, Depression, Prevalence, Systematic Review, Meta-analysis

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Key Messages

Clinically, significant depressive symptoms affected half of the people with extremely short prognoses. Results provide clinicians, policymakers and funders, researchers, and the general public with new information about the high prevalence of clinically significant depressive symptoms in the last days to weeks of life, highlighting the need for proactive recognition, assessment, and management.

Introduction

Depression is a complex and debilitating condition often seen in the people with advanced life-limiting illnesses. For individuals affected at the end-of-life, clinical depression can amplify suffering, limit capacity for pleasure, meaning, and engagement with their loved ones.[1–3] It may also be associated with a desire for hastened death.[4]

Assessing and managing depressive symptoms in the setting of advanced life-limiting illnesses can be complex. A key factor in the complexity stems from the amorphous use of the terminologies of "depression" and "palliative care population" in the literature. In fact, this term "depression" can imply: 1) a symptom of low-mood state; 2) depressive syndromes consisting of a collection of low-mood related symptoms (e.g., guilt, suicidal ideation, or anorexia) secondary to various mental disorders; or 3) specific depressive disorders (e.g., major depressive disorder) defined by the gold-standard diagnostic criteria.[5] These diagnostic criteria include Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases and Related Health Problems for depressive disorders (ICD).[6–9] Meanwhile, the studied "palliative care population" can differ significantly from one study to another because of the absence of a standardized referral system for palliative care.[10] The heterogeneity of definitions and the numerous assessment methods across the literature complicate the assessment and management of depression at the end-of-life. These have contributed to the wide range of depression prevalence (2%–30%) found in the general population with advanced life-limiting illnesses.[2,3,11–18]

The recognition, assessment, and management of depressive symptoms are even more challenging in the subset of the palliative population who are in the last days to weeks of life.[19,20] This period is usually characterized by an increasing dependence on others for care, increasing symptom burden, and declining functional scores indicative of one month or less of median survival.[19,21] These include: Karnofsky Performance Scale (KPS) ≤ 40, Eastern Cooperative Oncology Group (ECOG) 4, and Palliative Performance Scale ≤ 50.[19,22,23] Frailty and associated symptoms (such as severe fatigue, hypersomnia, and physical weakness) may make it difficult for clinicians to recognize and assess depressive symptoms, especially in people presenting with depressive disorders for the first time.[3] In this setting, treatment can also be challenging. Psychological therapies may require adaptation as the patients' cognition might be impaired with poor concentration or delirium, whereas their energy levels and motivation are often limited.[19,24,25] Engagement in therapy may be too tiresome for some individuals and the benefits of the therapy may not manifest in time.[25] Typical oral antidepressants might not work soon enough because of the person's extremely short prognosis,[26] or cannot be swallowed because of frailty.[25] Therefore, some clinicians feel a sense of futility in assessing and managing depressive symptoms of these individuals.[20]

As this subset of the palliative population with extremely short prognoses and clinically significant depressive symptoms has specific challenges and needs, it is important to define its prevalence. Previous systematic reviews of the prevalence of depressive symptoms in the palliative care and oncology settings did not explicitly examine prevalence in people with extremely short prognoses.[11,12] In addition, studies included in these reviews focused on specialist palliative care and oncology cohorts.[11,12] Patients with advanced life-limiting illnesses and extremely short prognoses not known to these services would have been excluded.

For the purpose of this review, consistent with the literature, the term "clinically significant depressive symptoms" has been used. This term embraces various depressive conditions defined by 1) diagnostic criteria, such as ICD or DSM,[27] and 2) validated depression-specific screening tool.[28–30] It does not include delirium with depressive features. The inclusion of prevalence defined by depression-specific screening tools would ensure that subsyndromal depression are accounted for—that is clinically significant depressive symptoms that fulfill specific cut-offs of screening tools but not the conventional diagnostic criteria.

Knowledge of the prevalence of clinically significant depressive symptoms in people with extremely short prognoses would quantify its global burden and inform screening, assessment, and impetus for developing targeted therapies.

Aim

To determine the prevalence of clinically significant depressive symptoms in people with extremely short prognoses (median survival of ≤4 weeks with absolute cut-off of <2 months) suffering from advanced life-limiting illnesses, as indicated by survival or functional

status data (Karnofsky Performance Scale [KPS] ≤40 or equivalent).[22,23,31,32]

Methods

Design and Protocol Registration

Systematic review and meta-analysis were reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[33] This review focusing on prevalence studies represented the first part of the systematic review protocol prospectively registered in PROSPERO (CRD42019125119).

Search Strategy

A systematic search of the electronic databases of MEDLINE (OVID), PsycINFO, Embase, CINAHL, and CareSearch (CareSearch filter utilized via PubMed) for studies published between January 1994 and February 2019 was performed (last search February 27, 2019). The search was limited to the last 25 years, as 1994 was the year when DSM-IV was assimilated to ICD-10 to ensure congruence.[34]

The search strategy included search terms in the domains of [Palliative Care or Advanced Life-Limiting Illnesses] AND [Prevalence] AND [Depression] was used initially in MEDLINE (OVID). The search terms were then adapted for other electronic databases accordingly (see "Search Strategy" in Supplementary File 1).

Inclusion criteria for studies were: any setting of care or study design; adults (≥18 years) with advanced life-limiting illnesses and extremely short prognoses in the range of days to weeks defined by either survival data (absolute survival of <2 months) or functional status indicative of a median survival of 1 month (equivalent of AKPS ≤ 40 or Eastern Cooperative Oncology Group (ECOG) 4);[22,23,31,32] and prevalence of clinically significant depressive symptoms defined by a validated tool (e.g., Hospital Anxiety and Depression Scale [HADS]) or a depressive disorder defined by diagnostic criteria (DSM or ICD or equivalent). In relation to diagnostic criteria, the term "major/minor depression" will be used in this review to encompass 1) both "major/minor depressive disorders" and "major/minor depressive episodes" in DSM[6,7] and 2) "major/minor depression" in ICD.[8,9]

Excluded studies were those not peer-reviewed (e.g., theses); studies with no validated method of assessing depressive symptoms; studies using measures not specific to depression (e.g., Edmonton Symptom Assessment Scale); as well as systematic reviews and meta-analyses, case studies, opinion papers, editorials, study protocols, or guidelines. A manual selection for adult, human, and English studies was performed without the use of filters to minimize the risk of missing articles due to delayed coding issues. The reference lists of relevant systematic reviews and meta-analyses were hand-searched for eligible studies.

Study Selection

Search results were imported into Endnote X9.2 for duplicate removal, and subsequently exported to Covidence for title and abstract, and full-text screenings.[35,36]

Each study was reviewed by both the primary investigator (W. L.) and a reviewer from the alternative reviewer group (M. P., C. S., E. L., A. H., D. P., M. A., and S. K.). Fortnightly calibration session was held to maintain inter-rater reliability. Reasons for exclusions at full-text review were documented. A third independent reviewer (B. D.) was involved in resolving conflict.

Data Extraction

Data extracted from individual studies included country; study design; eligibility of sampled population; settings; diagnoses; participant demographics; sampling method; definition and number of participants with extremely short prognoses; depression definition, assessment timing and method; and number and prevalence of clinically significant depressive symptoms in people with extremely short prognoses. When necessary, the authors of the publications were contacted for clarification of the data.

Quality and risk of bias assessments were performed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools for use in JBI Systematic Reviews—Checklist for Prevalence Studies (for individual studies)[37,38] and the principles of Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (across studies).[39,40]

The primary investigator (W. L.) extracted data from all included studies. Alternative reviewers (M. P. and A. H.) checked the validity of extracted data and independently performed quality/bias assessment of studies by randomly selecting studies using a random number generator. Given that 100% consensus was reached on discussion after randomly reviewing 5 of the 13 studies, remaining studies were only reviewed by the primary investigator (W. L.).

Data Synthesis

Prevalence rates were calculated from the number of cases with clinically significantly depressive symptoms and extremely short prognoses over total number of cases with extremely short prognoses in each included study. Random effects models were used in accordance with the method of Nyaga et al. to produce pooled prevalence estimates for clinically significant depressive symptoms defined by specific screening tools and diagnostic criteria.[41,42] The I^2 statistics were used to estimate heterogeneity and risk of bias. Potential sources of heterogeneity were further

investigated by the use of visual inspection of the data, forest plots, and through meta-regression analysis. Inverted funnel plots and Egger's tests were performed to assess for small study effects or publication bias. Analyses were carried out with the function for proportion meta-analysis in STATA Version 16.0.

Results

As outlined in the PRISMA diagram (Figure 1), 7957 studies were identified through the electronic databases. After removal of duplicates, 5531 studies underwent title and abstract screening, leaving 500 studies for full-text screening. Following this, 13 studies (Table 1) were included for data extraction, with 57.1% (278 out of 487) full-text screening studies not having data on the subgroup of interest (people with extremely short prognoses). Handsearching did not identify any eligible studies.

Study demographics are illustrated in Table 2. All 13 included studies had a prospective design, with 5 studies[43–47] being longitudinal and 8 being cross-sectional only.[4,48–54] Two studies had a combination of malignant and nonmalignant diseases (e.g., cardiovascular, respiratory, and other diseases).[52,54] Ten studies focused on malignant disease only.[4,43,44,46–51,53] Out of these, one study focused on advanced gynecological cancer[53] and another on lung cancer.[46] Other eight malignant studies involved a combination of various types of cancers.[4,43,44,47–51] Extraction of data of interest from specific malignant or nonmalignant conditions in studies involving combination of conditions was not possible. Only one study focused exclusively on a nonmalignant disease (late stage amyotrophic lateral sclerosis).[45]

Six studies involved inpatients only,[4,43,47,48,53,54] of which three were palliative care specific.[4,47,53] One study was home care only (palliative care specific).[52] Four studies were mixed settings,[44,49–51] one of which was palliative care specific.[49] Two studies did not specify the setting of care.[45,46]

Mean age reported in eight studies ranged from 58.0 to 70.9 years old. Five studies did not report mean age. The percentage of males ranged from 36.5% to 69.8% in 11 studies. One study did not report participant gender,[44] and one study only recruited females with advanced gynecological cancers.[53]

For the definition of extremely short prognoses, seven studies reported functional status equivalent of

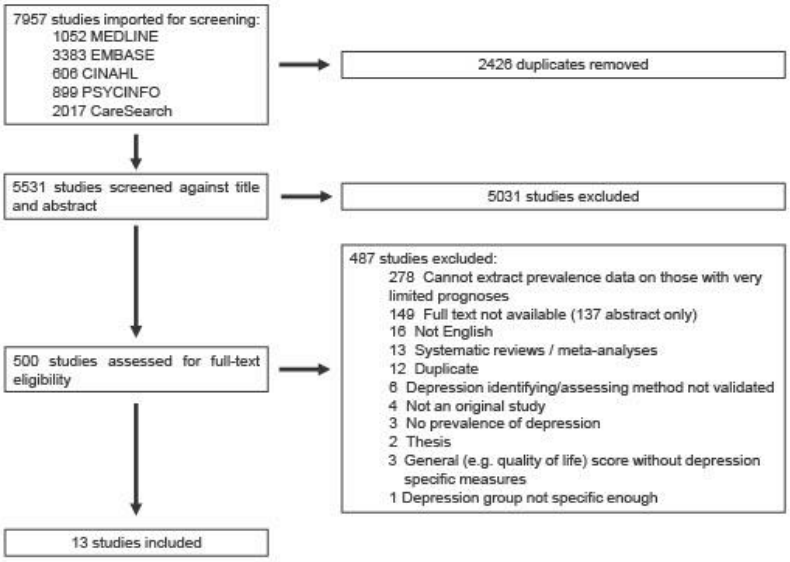

Fig. 1. PRISMA Flow Diagram.[33] A total of 7957 studies were identified through the electronic databases. After removal of duplicates, 5531 studies underwent title and abstract screening, leaving 500 studies for full-text screening. Following this, only 13 studies were included for data extraction. Out of the 478 articles excluded: 57.1% (278 out of 487) of full-text screening studies did not have data on the subgroup of interest (people with extremely short prognoses); 149 articles had no full text (majority were abstracts or posters only); 16 were not English; 13 were systematic reviews/meta-analyses; 12 were further duplicate identified; 4 were not an original study; 3 had no prevalence of depression; 2 were thesis; 3 were general score without depression specific measures; and 1 study had depression group not specified well enough.

Table 1
Characteristics of Included Studies

Author Year	Location, Country	Study Design	Source Population Eligibility/Recruitment Setting	Diagnoses	Demographics of Source Population (Total Number [*N*], Age, Gender)	Sampling Method	Definition of Extremely Short Prognoses/ Number from Source Population	Depression Definition/ Assessment Timing and Method	Number (*n*) and Prevalence (%) of Clinically Significant Depressive Symptoms in People with Extremely Short Prognoses
Alamri et al. 2017[54]	Jeddah, Saudi Arabia	Prospective Cross-sectional Prevalence Study	Elderly patients aged 60 years and older admitted to the medical (51%) and surgical wards (49%) of a single university hospital Exclusion: severe cognitive dysfunction, acute psychosis, bipolar disorder, schizophrenia, language barrier, aphasia, hearing impairment, reduced level of consciousness, or unstable medical illnesses	Cancer (not otherwise specified) and mixed nonmalignant diseases (cardiovascular, gastrointestinal, genitourinary, infectious, metabolic-endocrine, musculoskeletal, neurological, respiratory, and other)	*N* = 200 Mean age: 70.2 (SD: 8.1) Male = 41.0%	Consecutive	Hospital mortality/ Survival (author responded in email stating all those with hospital mortality had survival <60 days) *N* = 19	1. Self-administered PHQ-9: • ≥10: "major depression" • ≥ 5–9: "other depressive disorders" 2. Structured clinical interview with DSMV for "major depressive disorder" Within 48 hours of hospital admission by a trained research team member	PHQ-9 ≥ 10: *n* = 6 (31.6%) PHQ-9 ≥ 5–9: *n* = 2 (10.5%) DSMV Major Depressive Disorder: *n* = 1 (5.3%)
Breitbart et al. 2000[4]	New York, United States	Prospective Cross-sectional Prevalence study	Hospitalized, terminally ill patients with cancer recruited after admission to a 200-bed palliative care hospital with life expectancy of less than six months Inclusion: English speaking; sufficiently cognitively intact to provide informed consent and valid data; and were not considered likely (by their physician) to suffer psychological harm from participation Exclusion: Mini-Mental State Examination score below 20	Cancer (not otherwise specified)	*N* = 92 Mean age: 65.9 (SD: 15.6) Male = 40.0%	Unclear	Survival with average time until death was 28 days *N* = 89 (interviews could not be completed for three subjects)	DSMIV for "major depressive episode" After admission jointly by two investigators via structured clinical interview (interrater reliability coefficients 0.55)	DSMIV major depressive episode: *n* = 15 (16.9%)

(*Continued*)

Table 1
Continued

Author Year	Location, Country	Study Design	Source Population Eligibility/Recruitment Setting	Diagnoses	Demographics of Source Population (Total Number [*N*], Age, Gender)	Sampling Method	Definition of Extremely Short Prognoses/ Number from Source Population	Depression Definition/ Assessment Timing and Method	Number (*n*) and Prevalence (%) of Clinically Significant Depressive Symptoms in People with Extremely Short Prognoses
Chan et al. 2012[53]	Hong Kong, China	Prospective Cross-sectional study	Adult patients (≥18 years) with advanced (Stage III-IV) gynecological malignancy in the palliative phase admitted to the palliative care unit of Grantham Hospital, Hong Kong Inclusion: Chinese descent; fluent in the Cantonese dialect; and being capable of giving informed consent to participate in the study Exclusion: Unable to complete the questionnaires due to either physical or cognitive limitation; and being unable to communicate either verbally or in writing	Gynecological cancers (ovary, cervix, uterus)	*N* = 53 Mean age: 62.1 (SD: 15.5) Male = 0%	Consecutive	Functional status: median PPS = 40 *N* = 53	HADS (Chinese Cantonese version — Cronbach's α = 0.77): • 8 to 10: "doubtful case" • 11 or higher: "definite case" • 15 or higher: "severe depression" Within 3 days of admission interviewed by principal investigator	HADS score: • 11 or higher "definite case": *n* = 33 (62.2%) • 15 or higher "severe depression": *n* = 10 (19%)
Chochinov et al. 1995[47]	Winnipeg, Canada	Prospective longitudinal prevalence study	Terminal cancer adult patients from palliative care units of two hospitals in Winnipeg, Canada Exclusion: Cognitively impaired and unable to give informed consent or were too gravely ill to take part in a detailed interview	Mix cancer types (lung, gastrointestinal, genitourinary breast, hematological and other)	*N* = 200 Mean age: 70.9 (SD: 10.6) Male = 48.5%	Unclear	Survival: Median of 43 days Functional status: mean KPS 40 *N* = 200	DSMIIIR: Major and Minor Depressive Episodes One week or more after admission using semistructured diagnostic interview administered by a trained psychiatric nurse, clinical psychologist or a psychiatrist. Two-week follow-up	DSMIIIR: • Major depressive episode: *n* = 16 (8%) • Minor depressive episode: *n* = 9 (4.5%) Cannot extract prevalence data of extremely short prognosis on the two-week follow-up time point (as only those with desire for death were re-assessed and reported).

								interview conducted only for those with desire to die at the initial interview. Inter-rater reliability measured by having second rater attend 13.5% of random sample interview (kappa 0.76).	
Fisher et al. 2014[52]	Ontario, Canada	Prospective Cross-sectional Prevalence Study	Home care palliative care adult patients in 6 of 14 sites in Ontario involved in pilot implementation of new palliative care need assessment tool (InterRAI Palliative Care) with a mix of malignant and nonmalignant diseases "Participants were classified as palliative by the home care case manager if they were no longer responsive to curative treatment, considered to be dying, and the goal of care was to alleviate distressing symptoms in the last stage of their illness" Exclusion: Significant cognitive impairment (i.e., Cognitive Performance Score [CPS] < 4); Unable to give informed consent	Cancer (not otherwise specified) and non-malignant diseases (Cardiovascular, Chronic Obstructive Pulmonary Disease, and other)	$N = 5144$ Average age of 70.0 (range: 19.6–107.2; two-thirds of the sample > age 65) Male = 49.1%	Unclear	Survival: Estimated prognosis <6 weeks $N = 358$	Depression Rating Scale (DRS) (InterRAI Palliative Care) ≥ three for "Depressive Symptoms" Assessor rating at time of assessment not otherwise specified	*Table 1*: "Depressive Symptoms" by Depression Rating Scale (DRS) (InterRAI Palliative Care) ≥3: $n = 74$ (20.7%)
Hartung et al. 2017[51]	5 regions across Germany	Prospective Cross-sectional Prevalence study	Adults (age 18 through 75), proficient in German, with cancer from a mixture of clinical	Mix cancer types (thyroid, brain, pancreas, hematological, female genital	$N = 4020$ Mean age: 58 (SD: 11) Male = 48.6%	Consecutive	Functional status: ECOG4 $N = 13$	PHQ-9 ≥10 for "depressed" (German version of the self-report measure)	"Depressed" by PHQ-9 ≥ 10: $n = 6$ (46.2%)

(*Continued*)

Table 1
Continued

Author Year	Location, Country	Study Design	Source Population Eligibility/Recruitment Setting	Diagnoses	Demographics of Source Population (Total Number [*N*], Age, Gender)	Sampling Method	Definition of Extremely Short Prognoses/ Number from Source Population	Depression Definition/ Assessment Timing and Method	Number (*n*) and Prevalence (%) of Clinically Significant Depressive Symptoms in People with Extremely Short Prognoses
			settings—total of 84 inpatient oncology wards, outpatient clinics, cancer rehabilitation centers in five distinct regions across Germany (Freiburg, Hamburg, Heidelberg, Leipzig and Würzburg) Exclusion: Cognitive and verbal impairments that interfered with ability to give informed consent	organs, bladder, lung, stomach/ esophagus, head and neck, soft tissue, breast, testis, kidney/ urinary tract, colon/rectum, hepatobiliary, melanoma, prostate, other)				Timing of assessment not specified	
Hopwood & Stephens 2000[46]	United Kingdom	Prospective – Longitudinal Prevalence Study using data from 3 RCTs	Adults with lung cancer (non-small-cell and small-cell lung cancers) from three multicentred RCTs by United Kingdom Medical Research Council Lung Cancer Working Party: two chemotherapy trials (LU12 and LU16) and one radiotherapy trial (LU13)	Non-small-cell and small-cell lung cancers	$N = 1189$ (Male = 69.8%), consisted of the below: LU12 (Chemotherapy trial for small-cell lung cancer): $N = 510$ Median age: 65 (Range 39–90) Male = 63% LU 16 (Chemotherapy trial for small cell lung cancer) $N = 370$ Median age: 67 (Range 35–83) Male = 63% LU13 (Radiotherapy trial for Non-small-cell-lung cancer) $N = 509$ Median age: 66 (Range: 33–89) Male = 79%	Random	Functional status: WHO PS 4 $N = 11$	HADS for "Depression" ("Borderline" or "Case"): • 8–10: "Borderline" • ≥11: "Case" HADS assessed at baseline and at first follow-up	"Depression" (case or borderline score) by HADS ≥8 at baseline: $n = 6$ (55.0%) Cannot extract data of extremely short prognosis on the first follow-up time point (High attrition rate with WHO PS 4 prevalence data not reported)

Que et al. 2013[50]	Manila, Philippines	Prospective Cross-sectional Prevalence Study	Adults oncology inpatients and outpatients presented for cancer treatment at a single nonprofit tertiary hospital in Manila, Philippines	Mixed Cancer Types (breast, head and neck, lung, brain, lymphoma, leukemia)	$N = 271$ Age ≥ 53 = 53.5% Male = 36.5% (Age & Gender data extrapolated from *Table 2* of article)	Unclear	Functional status: ECOG 4 $N = 7$	"Depression" by PHQ-8 (excludes the item on suicidal ideation) ≥10 (Cronbach's α = 0.84) Timing of assessment (survey) not specified	"Depression" by PHQ-8 ≥10: $n = 6$ (86%)
Rabkin et al. 2005[45]	New York, US	Prospective Longitudinal Prevalence Study	Hospice eligible adult patients with late stage amyotrophic lateral sclerosis (ALS) indicated by FVC < 50% (*a value related to the risk of hospice admission and death or the need for mechanical ventilation within 6 months") from multiple sites (though 94% enrolled from a single ALS Research Center) (setting not otherwise specified) Exclusion: dementia; inability to speak English; absence of nonpaid caregiver who agreed to participate; use of mechanical ventilation at baseline; inability to communicate at least "yes" and "no"; lived outside three-hour drive from medical center	Late-stage amyotrophic lateral sclerosis	$N = 80$ Age ranged from 27 to 85, 20% were under age 50, and one-third were over 70 Male = 56%	Unclear	Survival: Median interval between time of last monthly interview and death = 30 days $N = 53$	Major and Minor Depression by PHQ-9: • Major Depression: ≥5 items with score ≥2 with ≥1 item being depressed mood or anhedonia • Minor Depression: ≥3 items with score ≥2 with ≥1 item being depressed mood or anhedonia Authors departed from the standard scoring on three items of PHQ-9 that were sometimes directly caused by ALS: sleep problems, poor appetite, and psychomotor retardation when considered inappropriate, and prorated the remaining items to generate a total score. Scheduled monthly interviews almost always at home until patients met a study endpoint	Depression (Both major and minor Depression) by PHQ-9≥6: $n = 17$ (32.1%)

(*Continued*)

Table 1
Continued

Author Year	Location, Country	Study Design	Source Population Eligibility/Recruitment Setting	Diagnoses	Demographics of Source Population (Total Number [*N*], Age, Gender)	Sampling Method	Definition of Extremely Short Prognoses/ Number from Source Population	Depression Definition / Assessment Timing and Method	Number (*n*) and Prevalence (%) of Clinically Significant Depressive Symptoms in People with Extremely Short Prognoses
								of tracheostomy or death	
Rabkin et al. 2009[44]	New York/San Francisco, United States	Prospective Longitudinal Prevalence Study	Patients with cancer with prognosis of 6–12 months from oncology services of multiple sites and home care service of a community hospital Exclusion: Non-English speaking; insufficient cognitive capacity to consent to study; had no a family member or close friend who served as a nonpaid caregiver and who agreed to participate; not lived at home within an hour drive from the respective medical center at study entry	Mixed cancer types (breast, lymphomas, colorectal, lung, pancreas and other)	$N = 58$ Age and gender of the cohort not reported	Convenience	Survival: Median interval between final assessment and death = 28 days $N = 24$	"Major depressive disorder" by PHQ-9 ≥10: (≥ five items including depressed mood or loss of interest must be scored 2 or 3) (Cronbach α = 0.79) Assessment by interviews almost always at home scheduled at approximately 1-month intervals until death or the study ended	Major depressive disorder by PHQ-9 ≥10: $n = 7$ (29.2%)
Stromgren et al. 2002[49]	Copenhagen, Denmark	Prospective Feasibility/ Cross-sectional Prevalence study	Danish speaking adult patients with advanced cancer for which no curative or life-prolonging treatment could be offered and referred/admitted to the palliative care services of a Copenhagen hospital (mixture of inpatient, outpatient and home care palliative care services) Exclusion: No informed consent;	Mixed cancer types (brain, head and neck, gastrointestinal tract, respiratory, breast, genitourinary, gynecological, sarcoma, melanoma/skin, hematologic, unknown)	$N = 176$ Age: mean 62.9 (No SD reported); median 63 (Range: 37–91) Gender: Male = 43.8%	Consecutive	Survival from first contact with department: Median 35 days Functional status: Median KPS 40 $N = 134$	"Depression (Definite case)" by HADS ≥ 11 Assessed via self-assessment questionnaire at first contact with the palliative care department	Depression (Definite case) by HADS ≥ 11: $n = 65$ (47.0%)

			staff judged the patient too ill to participate						
Tang et al. 2016[43]	Taiwan	Prospective Longitudinal prevalence study	Adult (≥20 years old) oncology patients with terminal stage cancer and palliative intent treatment (unresponsive to curative cancer treatment and continuing to progress) from medical inpatient units of a medical center in Taiwan Exclusion: Cognitively incompetent as evaluated by their primary physicians; ability to communicate coherently with data collectors	Mixed cancer types (lung, liver-pancreas, head and neck, other)	*N* = 325 Age over 56 years old = 58.5% Male = 57.5%	Convenience	Survival - Time before death of 1–30 days *N* = 233	"Severe Depressive Symptoms" by HADS scores ≥11 Participants were interviewed while hospitalized or waiting for outpatient visits approximately every two weeks until they declined to participate or died	"Severe Depressive Symptoms" by HADS scores ≥11: *n* = 192 (82%)
Zhao et al. 2014[48]	Beijing, China	Prospective Cross-sectional Study	Consented adult (≥18 years) patients with cancer from the inpatient oncology ward of a hospital in Beijing Exclusion: Too frail or unwell to be interviewed; obvious cognitive impairment based on a brief clinical interview performed immediately before the administration of the Mini International Neuropsychiatric Interview (MINI) 5.0; severe hearing/speech impairment that would make the interview infeasible; being unaware of cancer diagnoses	Mixed cancer types (lung, digestive tract, breast, liver, ovarian, uterine and other)	*N* = 460 Mean age: 59.4 (SD: 12.0); Range: 20–99 Male = 49.1%	Consecutive	Functional status: ECOG 4 *N* = 51	"Depressive Disorders" by DSMIV ascertained by Chinese version of the Mini International Neuropsychiatric Interview (MINI) 5.0 by eight trained psychiatrists (coefficients of interrater and test–retest reliability were 0.92 and 0.98 respectively). Depressive disorders included: major depressive disorder (MDD), dysthymia, minor depressive disorder, mood	"Depressive Disorders" by DSMIV (MINI): *n* = 24 (47.1%) Depressive disorders included: major depressive disorder (MDD), dysthymia, minor depressive disorder, mood disorder due to a general medical condition with major depressive-like episode or with depressive features; and mood disorder due to substances with depressive features.

(*Continued*)

Table 1
Continued

Author Year	Location, Country	Study Design	Source Population Eligibility/Recruitment Setting	Diagnoses	Demographics of Source Population (Total Number [*N*], Age, Gender)	Sampling Method	Definition of Extremely Short Prognoses/ Number from Source Population	Depression Definition/ Assessment Timing and Method	Number (*n*) and Prevalence (%) of Clinically Significant Depressive Symptoms in People with Extremely Short Prognoses
								disorder due to a general medical condition with major depressive-like episode or with depressive features; and mood disorder due to substances with depressive features. Time of assessment by psychiatrists while as inpatients was not otherwise specified.	

ALS = amyotrophic lateral sclerosis; CPS = cognitive performance score; DRS = Depression Rating Scale (InterRAI Palliative Care); DSM = Diagnostic and Statistical Manual of Mental Disorders; ECOG = Eastern Cooperative Oncology Group Performance Status; FVC = forced vital capacity; HADS = Hospital Anxiety and Depression Scale; KPS = Karnofsky Functional Performance Status Scale; MDD = major depressive disorder; MINI = Mini International Neuropsychiatric Interview; PHQ = Patient Health Questionnaire; PPS = Palliative Performance Scale; PHQ = Patient Health Questionnaire; RCT = randomized controlled trial; SD = standard deviation; WHO PS = World Health Organization Performance Status.

Table 2
Study Demographics of Included Studies ($n = 13$)

Study Characteristics	Number of Studies (n out of 13)/Study Descriptions
Study Design	
Prospective	13
Longitudinal[43–47]	5
Cross-sectional[4,48–54]	8
Country	
Saudi Arabia[54]	1
Philippine[50]	1
China (Beijing/Hong Kong/Taiwan)[43,48,53]	3
United States[4,44,45]	3
Canada[47,52]	2
United Kingdom[46]	1
Germany[51]	1
Denmark[49]	1
Recruitment Settings	
Inpatient only	6
General[43,48,54]	3
Palliative care specific[4,47,53]	3
Outpatient only	0
Home care only	1
General	0
Palliative care specific[52]	1
Mixed settings	4
General[44,50,51]	3
Palliative care specific[49]	1
Others	2
Setting not otherwise specified[45,46]	2
Diagnoses	
Combination of malignant and non-malignant conditions[52,54]	2
Malignant only[4,43,44,46–51,53]	10
Combination of early and advanced cancer types[50,51]	2
Advanced/terminal cancer (mix types)[4,43,44,47,49,54]	6
Advanced gynecological cancer (palliative phase)[53]	1
Lung cancer (small cell & non-small cell) on palliative chemo/radiotherapy[46]	1
Non-malignant	1
Late stage amyotrophic lateral sclerosis[45]	1
Age	
Mean age	58–70.9 among nine studies[4,47–49,51–54] (five studies did not report mean age)
Gender	
Male %	36.5%–69.8% (11 studies) (one study has 0% male (gynecological cancer study;[53] and one study did not report gender[44])
Definition of Extremely short prognoses	
1. Functional status[46–51,55,a]	7
ECOG4[48,50,51]	3
WHOPS4[46]	1
PPS≤50[53]	1
KPS≤40[47,49]	2
AKPS≤40	0
2. Survival[4,43–45,47,49,52,54,a]	8
Days prior to death[43,52,54]	3 (Range: 1–60 days)
Average survival (days)[4,44,45,47,49]	5 (Range: 28–43 days—medians used apart from one study where average is reported but the type not specified[4])
Definition of Clinically Significant Depressive Symptoms	
1. Tools[43–46,49–54,c]	10
PHQ[44,45,50,51,54]	5
PHQ9[44,45,51,54]	4
Score≥10 as major depression[44,45,51,54]	4
Score 5–9 as other depressive disorders[45,54,b]	2
PHQ8≥10 (no suicide item)[50]	1
HADS[43,46,49,53]	4
HADS≥11 as depression[43,46,49,53]	4
HADS≥8 as borderline depression[46]	1
DRS≥3 (InterRAI PC)[52]	1
2. Criteria[4,47,48,54,c]	4
DSM[4,47,48,54]	4

(*Continued*)

Table 2
Continued

Study Characteristics	Number of Studies (*n* out of 13)/Study Descriptions
DSMV[54]	1
DSMIV[4,48]	2
DSMIIIR[47]	1
ICD	0
Endicott	0
3. Conditions by DSM[4,47,48,54]	4
Major depressive disorder/episode[4,47,48,54]	4
Minor depressive disorder/episode[47,48]	2
Dysthymic disorder[48]	1
Mood disorder due to general medical condition with depressive features[48]	1

[a]Two studies had both functional status/survival.[47,49]
[b]Rabkin et al., 2005 uses 3 or more PHQ9 items with score ≥2 as minor depression.[45]
[c]One study had both DSMV + PHQ9.[54]

AKPS ≤40 (median survival of one month),[46–51,53] and eight studies reported directly on survival data.[4,43–45,47,49,52,54] Two studies reported both survival and functional status data.[47,49]

Ten studies defined clinically significant depressive symptoms using a specific tool: Patient Health Questionnaire 8 or 9 (PHQ-8 or 9; $n = 5$),[44,45,50,51,54] HADS ($n = 4$),[43,46,49,53] and Depression Rating Scale [DRS] ($n = 1$).[52] Four studies used diagnostic criteria (DSMIIIR, IV or V),[4,47,48,54] whereas one study used both PHQ-9 and DSMV.[54]

Prevalence of Clinically Significant Depressive Symptoms

The prevalence of clinically significant depressive symptoms in people with life-limiting illnesses and extremely short prognoses was analyzed with reference to tools, diagnostic criteria, and risk of bias.

Tools

1. ≥Mild or Minor Severity (PHQ-8/9 ≥ 5, HADS ≥ 8, DRS ≥ 3)

Overall pooled prevalence of clinically significant depressive symptoms of mild/minor severity or greater (defined as: PHQ-8/9 ≥ 5, HADS ≥ 8, DRS ≥ 3;[55–57] $n = 10$)[43–46,49–54] in people with extremely short prognoses ($N = 905$) was 50% (95% CI: 29%–70%) (Figure 2). There was high heterogeneity ($I^2 = 97.6\%$).

Meta-regression found no significant differences between prevalence of depressive symptoms measured by different tools ($P = 0.774$). Differences in tools also did not account for the high heterogeneity among studies (adjusted $R^2 = -12.40\%$). Interestingly, DRS ≥ 3 appeared to yield lower prevalence of depressive symptoms of 21% (95% CI: 17%–25%; $n = 1$). Removal of the prevalence data from DRS ≥ 3 raised overall pooled prevalence to 53% (95% CI: 37%–70%) and reduced heterogeneity slightly ($I^2 = 93.1\%$) (extremely short prognoses sample: $N = 547$).

2. ≥Moderate or Major Severity (PHQ-8/9 ≥ 10, HADS ≥ 11)

When performing subgroup analyses on depressive symptoms with the severity cut-off of moderate or more (PHQ-8/9 ≥ 10 or HADS ≥ 11;[56,57] $n = 7$), pooled prevalence of clinically significant depressive symptoms in people with extremely short prognoses ($N = 476$) was 55% (95% CI: 37%–74%).[43,44,49–51,53,54] Heterogeneity was still high ($I^2 = 93.4\%$) (prevalence data from DRS ≥ 3 were not included in subgroup analysis as DRS ≥ 3 contained both major and minor depressive symptoms).[55]

There was no statistically significant difference ($P = 0.36$) between pooled prevalence measured by PHQ-8/9 ≥ 10 (47% [95% CI: 23%–71%]) and that by HADS ≥ 11 (64% [95% CI: 40%–89%]), accounting for only 4.2% of the study heterogeneity in the greater or equal to moderate severity subgroup (meta-regression adjusted $R^2 = 4.2\%$).

Common Disorders by DSM Diagnostic Criteria

Prevalence of depressive symptoms defined by common disorders through diagnostic criteria (DSMIIIR/IV/V) included

- Major depression (major depressive disorder/episode; $n = 3$):[4,47,54]
  - On meta-analysis, the pooled prevalence of major depression in people with extremely short prognoses ($N = 308$) was 10% (95% CI: 4%–16%; extremely short prognoses sample size: $N = 308$; Figure 3).
  - Heterogeneity among studies was only moderate ($I^2 = 57.5\%$).
- Minor depression ($n = 1$):[47] 5% (95% CI: 2%–8%; extremely short prognoses: $N = 200$).

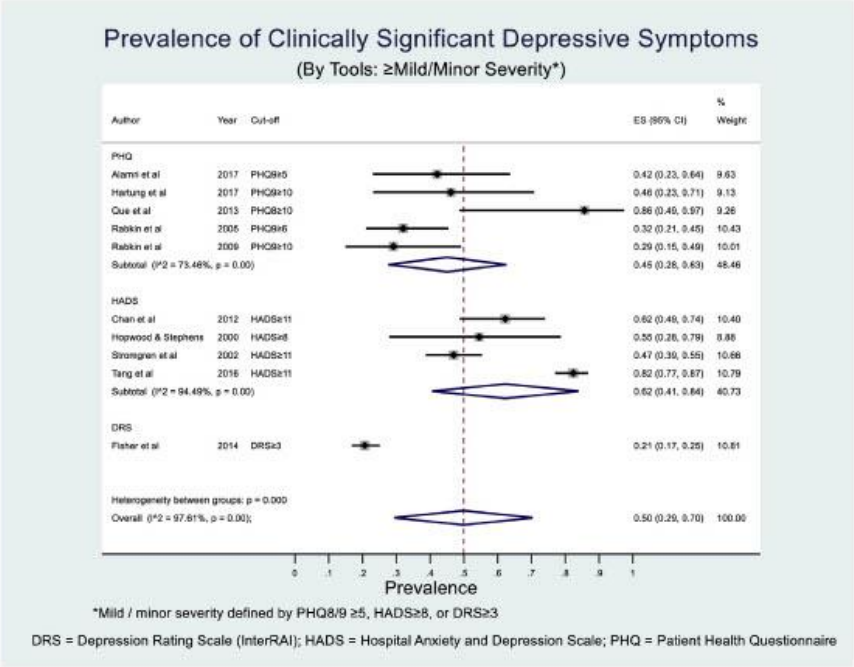

Fig. 2. Prevalence of clinically significant depressive symptoms in people with advanced life-limiting illnesses and extremely short prognoses identified by depression-specific screening tools. Overall pooled prevalence of clinically significant depressive symptoms of mild/minor severity or greater (defined as: PHQ8/9 ≥ 5, HADS ≥ 8, DRS ≥ 3 (55–57); $n = 10$)[45–46,49–54] in people with extremely short prognoses ($N = 905$) was 50% (95%CI: 29%–70%). Heterogeneity was high ($I^2 = 97.6\%$). For the subgroup with moderate severity or more (PHQ8/9 ≥ 10 or HADS ≥ 11(56, 57); $n = 7$): Pooled prevalence was 55% (95%CI: 37%–74%; $N = 476$).[43,44,49–51,53,54] Heterogeneity was high ($I^2 = 93.4\%$).

Longitudinal Changes

In five longitudinal studies, data for longitudinal changes in prevalence of clinically significant depressive symptoms over the 3–6 months before death could be extracted in two studies.[43,44] Tang et al. reported increasing prevalence of clinically significant depressive symptoms (defined by HADS ≥11) in Chinese patients with cancer as days to death approached from 44.58% (181–365 days), 49.91% (91–180 days), 69.44% (31–90 days) to 82.64% (1–30 days).[43] Rabkin et al., also in the cancer population but in United States, reported a prevalence of major depression (using PHQ-9) of 0% at 3 months before death, rising to 29% in the last month of life.[44]

Two studies informed the proportion of new onset symptoms in those cases with clinically significant depressive symptoms and extremely short prognoses, which were 36.3% (four out of 11—Rabkin et al.) and 57.1% (four out of seven—Rabkin et al.).[44,45]

Quality/Risk-of-Bias Assessment

Quality of Individual Studies. Seven of thirteen studies did not fulfill at least one item of the JBI checklist (Figure 4). The leading source of bias (not fulfilling specified item criteria) was selection bias (item 1–5: 21.5%), followed by attrition bias (item 9: 15.4%), and detection/measurement bias (item 6–7: 3.8%). No analysis bias was identified.

Prevalence by Low Risk-of-Bias Studies. There were only two studies found to have low risk of bias, fulfilling all nine criteria in the JBI checklist of prevalence studies. These differed in country of study and method of depression identification.[48,49]

Despite these differences, they both had the same depression prevalence of 47%: Stromgren et al. (2002)—study from Denmark using the tool HADS ≥ 11 yielded 47% (95% CI: 39%–55%);[49] and Zhao et al. (2014)—study from China using DSMIV criteria

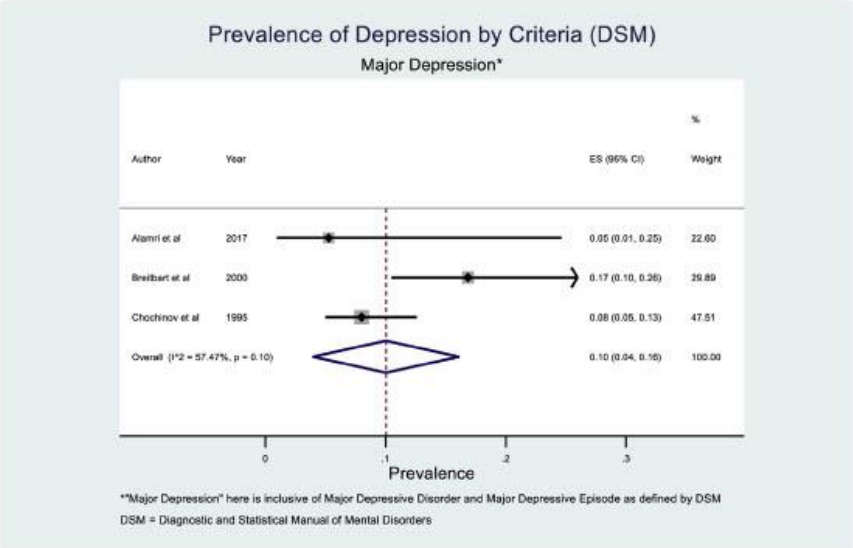

Fig. 3. Pooled prevalence of major depression in people with advanced life-limiting illnesses and extremely short prognoses ($n = 3$; extremely short prognoses $N = 308$). On meta-analysis, the pooled prevalence of major depression in people with extremely short prognoses ($N = 308$) was 10% (95%CI: 4%−16%; extremely short prognoses sample size: $N = 308$).[4,47,54]

for Depressive Disorders (major and minor depression, dysthymia, and mood disorders due to general medical conditions with depressive features) found 47% (95% CI: 34%−60%).[48]

Quality Across Studies. Each domain of Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess quality across studies (described in the following section). However, the overall quality score could not be generated using the online platform for GRADE (GRADEPro), as it was not configured for systematic reviews of prevalence studies.[40,58,59]

For risk-of-bias across studies, there were serious limitations due to the general selection bias intrinsic to researching populations with life-limiting illnesses. Participants were often excluded if they had significant cognitive impairment or frailty.

For the domain of indirectness, all studies directly addressed their research questions on the prevalence of depressive symptoms.

Regarding imprecision, there was a lack of established guidance in assessing precision for meta-analyses of prevalence studies. Assuming the use of the width of confidence intervention in the GRADE approach to assess precision, there was a relatively low precision for prevalence of depressive symptoms identified by tools (50% [95% CI: 29%−70%]). However, precision was modest for that identified by diagnostic criteria, with major depression having the widest confidence interval (10% [95% CI: 4% −16%]). If precision was defined as the sensitivity and specificity of tools used, then it was relatively high across the studies. All the tools used (PHQ, HADS, and DRS) have been psychometrically tested in the palliative care or oncology settings.[55,60–62]

For inconsistency, there was high heterogeneity across studies for the prevalence of depressive symptoms by tools ($I^2 = 93.4\%–97.6\%$) but only modest heterogeneity ($I^2 = 57.5\%$) for prevalence of depressive symptoms by diagnostic criteria for major depression.

To assess for small study effects and publication bias, studies with sample sizes of 100 or less were removed from meta-analyses. The final pooled prevalence estimates of clinically significant depressive symptoms by tools (≥mild severity) (50% [95% CI: 8%−92%]; $I^2 = 99.4$; $n = 3$[43,49,52]) and diagnostic criteria for major depression (8% [95% CI: 5.0%−12.6%]; $n = 1$[47]) have not changed significantly from the estimates that included all studies. Regression (Egger's) tests of the corresponding inverted funnel plots again showed no evidence of small study effects or publication bias for the meta-analyses that included all selected studies: using depression-specific screening tools (≥mild or minor severity; Egger's coefficient:

		JBI Checklist for Prevalence Studies (Items 1-9)*								
Study	Authors / Year	1	2	3	4	5	6	7	8	9
1	Alamri et al 2017	Y	Y	?	Y	N	Y	?	Y	?
2	Breitbart et al 2000	N	?	N	?	?	Y	N	Y	N
3	Chan et al 2012	Y	Y	?	Y	Y	Y	Y	Y	?
4	Chochinov et al 1995	N	?	Y	Y	N	Y	Y	Y	N
5	Fisher et al 2014	?	?	Y	Y	Y	Y	?	Y	?
6	Hartung et al 2017	?	Y	Y	?	?	Y	Y	Y	Y
7	Hopwood & Stephens 2000	N	Y	Y	N	N	Y	Y	Y	Y
8	Que et al 2013	?	?	Y	N	N	Y	?	Y	Y
9	Rabkin et al 2005	Y	?	Y	Y	Y	Y	Y	Y	Y
10	Rabkin et al 2009	N	N	N	Y	Y	Y	Y	Y	?
11	Stromgren et al 2002	Y	Y	Y	Y	Y	Y	Y	Y	Y
12	Tang et al 2016	Y	N	Y	Y	Y	Y	Y	Y	Y
13	Zhao et al 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y

*Joanna Briggs Institute Systematic Review Checklist for Prevalence Studies Items 1-9 (Options: 'Yes'; 'No'; 'Unclear'; and 'Not Applicable'):

1. Was the sample frame appropriate to address the target population?
2. Were study participants sampled in an appropriate way?
3. Was the sample size adequate?
4. Were the study subjects and the setting described in detail?
5. Was the data analysis conducted with sufficient coverage of the identified sample?
6. Were valid methods used for the identification of the condition?
7. Was the condition measured in a standard, reliable way for all participants?
8. Was there appropriate statistical analysis?
9. Was the response rate adequate, and if not, was the low response rate managed appropriately?

Overall appraisal: Include; Exclude; Seek further info (All 13 studies were included)

Fig. 4. Risk of bias assessment using Joanna Briggs Institute (JBI) Systematic Review Checklist for Prevalence Studies.[37,38] Seven out of thirteen studies did not fulfill at least one item of the checklist. Only two studies were found to have low risk of bias, fulfilling all nine criteria. The leading source of bias (not fulfilling specified item criteria) was selection bias (item 1–5: 21.5%), followed by attrition bias (item 9: 15.4%), and detection/measurement bias (item 6–7: 3.8%). No analysis bias was identified.

0.87 [95% CI: −7.45–9.19); $P = 0.815$), and diagnostic criteria for major depression (Egger's coefficient: 1.04 [95% CI: −36.12–38.21]; $P = 0.782$).

Discussion

High Prevalence of Clinically Significant Depressive Symptoms in Extremely Short Prognoses Setting

This evidence synthesis found high prevalence (one in two individuals) of clinically significant depressive symptoms in people with extremely short prognoses.

The duration of a median survival of one month (indicated by the functional scores of KPS ≤ 40 or ECOG = 4) with the upper limit of two months was used to differentiate individuals with extremely short prognoses from others with advanced life-limiting illnesses. This is an important distinction as this time period is the time during which frailty and symptomatology of the terminal illnesses (e.g., fatigue, delirium, and inability to swallow) significantly escalates, hindering effective depression assessment and management.[19,24,25] This extremely short life-expectancy period makes the conventional depression interventions unlikely to be successful due to their slow onset-of-actions, and supports the consideration for alternative rapid-onset interventions such as methylphenidate or ketamine.[26,63,64]

The prevalence of clinically significant depressive symptoms in advanced life-limiting illnesses using HADS score ≥11 have been reported in a systematic review to be around 29%.[11] This review adds to the data by finding a higher pooled prevalence of 50% in the subgroup with extremely short prognoses using depression-specific tools. If only studies with HADS score ≥11 were considered, an even higher overall pooled prevalence of 64% resulted, including the 47% from the low risk-of-bias study.[49]

Meanwhile, the prevalence of combined depressive disorders in the general advanced illness population using diagnostic criteria has been reported to be 25% in another systematic review.[12] This is lower than the corresponding prevalence of 47% found using diagnostic criteria in people with extremely short prognoses in the current review.[48] The higher prevalence of clinically significant depressive symptoms in those with extremely short prognoses is further supported by the findings of longitudinal studies by Tang et al. (included in this review) and Seow et al., where both studies reported increases of 33% and approximately 10%, respectively, in prevalence of clinically significant depressive symptoms in the last six months of life.[19,43]

Reasons for high prevalence of clinically significant depressive symptoms in people with advanced life-limiting illnesses and extremely short prognoses are likely multifaceted. In addition to individuals having the stressors of advanced life-limiting illnesses and associated adjustment issues, inadequacy of recognition, assessment, and management of these symptoms during life-limiting illnesses at earlier stages may be a factor. Studies reveal around 40% of clinicians treating people with advanced life-limiting illnesses do not regularly screen or assess for depressive symptoms, with as low as 7% of the depressed cases being recognized and up to 70% of affected individuals receiving inadequate interventions.[20,48,65–68] There is intrinsic difficulty in assessing depressive symptoms in individuals whose advanced life-limiting illnesses might mimic depressive symptoms, as well as challenges in providing interventions likely to be effective in time.[1,26] Further barriers to suboptimal recognition, assessment and management include: clinicians' fear of distressing patients, especially given the stigma associated with psychiatric diagnoses;[3,69] lack of awareness and skills to detect and manage depression;[20,68,70–75] perceived lack of resources such as time,[20,68,76] acceptable assessment tools and access to mental health services;[20,69,77–82] beliefs that depression is "normal";[69,76] and that screening and interventions are likely to be futile in this context.[70,71,73,83] It is possible that addressing these barriers might lead to an earlier detection and management of depressive symptoms in people with advanced life-limiting illnesses. This may subsequently lower the prevalence of such when prognoses are extremely short.

Meanwhile, evidence suggests a significant proportion of individuals with advanced life-limiting illnesses and extremely poor prognose were experiencing clinically significant depressive symptoms for the first time (36%–57% from Rabkin et al. and Rabkin et al. in this review[44,45]). This is also supported by the findings of a trend for building prevalence as death approaches.[43,44] Given the limitation of having only small number of studies with small sample sizes, these findings need to be interpreted with caution. The findings should not be perceived as definitive but hypothesis generating. The exact prevalence of new-onset cases needs to be further studied. Nonetheless, one might also ponder on the underlying drivers for having a substantial proportion of new cases of depressive symptoms in the last weeks to days of life. It may be possible that the pathological processes of the advanced life-limiting illnesses themselves such as brain metastases or hypercalcemia cause depressive symptoms.[84] Other potential drivers for new-onset depressive symptoms may be: the associated distressing symptoms and functional limitations that are often more marked toward the end-of-life caused by disease progression;[19,43,46,85] the associated grief and hopelessness;[86] loss of dignity;[87,88] concerns about social relationship (e.g., perceived lack of support or fear of being a burden to others);[43,47,85] and existential distress.[88] It would be instructive to see whether targeting these issues decreases incidence of depressive symptoms in people with extremely short prognoses in future studies.

Methods of Defining Clinically Significant Depressive Symptoms

The construct of "clinically significant depressive symptoms" in the literature is an interesting one. It encompasses depressive disorders diagnosed by the conventional diagnostic criteria.[27] It also includes subsyndromal depression where depressive symptoms are severe enough to fulfill certain thresholds set by various depression-specific screening tool but cannot be diagnosed as specific depressive disorders using diagnostic criteria.[27–30] In fact, the sole use of diagnostic criteria in assessing for depressive symptoms in the extremely short prognoses setting might underestimate the true prevalence of these symptoms. First, there may not be enough time for specific depressive disorder (e.g., two weeks for major depression[9]) to be established due to the short life expectancies.[89] Second, up to three-quarters of patients with extremely short prognoses might to excluded from studies, as the assessment of diagnostic criteria using psychiatric interviews could be too burdensome, considering their cognitive impairment or frailty[4,11,47]). The addition of using validated depression-specific screening tools in the palliative care setting to identify individuals with clinically significant depressive symptoms may overcome the issue of missing individuals with subsyndromal depression by diagnostic criteria. Nonetheless, the use of depression-specific tools does come with the intrinsic shortfall of "false-positivity." When used as indirect measurements of specific depressive disorders, normal anticipatory grief may not be entirely excluded, leading to an overestimation of the prevalence of specific

depressive disorders.[90,91] Perhaps, a better way to perceive the use of depression-specific screening tools is not to use them to predict for certain depressive disorders in this context. Rather, these tools have the value in identifying people who have clinically significant depressive symptoms at a certain time point that requires clinician attention and interventions, including those with subsyndromal depression.

There are a myriad of depression-specific screening tools. Among these, relatively few have been validated for use in the palliative care setting. These include: HADS, Single and Two Items Questions ("Are you depressed?" +/− "Have you lost interest in activities?"), Visual Analogue Scale, Edinburgh Postnatal Depression Scale, and Beck Depression Inventory-Short Form.[91] The present study identified three tools that were used in people with life-limiting illnesses and extremely short prognoses: Patient Health Questionnaire 8/9 (PHQ 8/9), HADS and Depression Rating Scale (DRS - InterRAI PC). This review and meta-analysis did not observe any statistical differences between them. This is consistent with the findings by Cameron and Hansson et al. that demonstrated similar prevalence of depressive symptoms generated by HADS and PHQ-9 with overall convergent validity between the two tools, though there was a lack of convergence between the severity cut-offs.[56,57] However, it is possible that, with only a modest number of studies using tools ($n = 10$), this study was insufficiently powered to detect the differences between them. Particularly, the one study that used DRS seemed to have yielded a low prevalence estimate.[52] The underlying reason might be due to the construct of DRS. The DRS was originally designed to detect depressive symptoms in nursing home residents, for whom assessing patients face-to-face using psychiatric interviews or self-reported depression-specific tools might be impractical.[55] Its scoring depends on the daily observed standardized mood and behavioral item data collected in the Resident Assessment Instrument, the Minimum Data Set.[55] Different from PHQ-8/9 or HADS, it only contains three depression-specific items (sad facial expression, tearfulness, and observed negative statements by residents [passive suicidal ideation]). Four other items are less depression-specific (anger and irritability, expressions of fears, repetitive health complaints, and repetitive anxious concerns).[55] Therefore, there is a possibility that DRS underrecognized depressive symptoms in patients who had other depressive symptom items included in PHQ-8/9 or HADS but did not have depressed or teary effect, leading to a lower prevalence estimate. The comparison and feasibility of these tools for the use of detecting clinically significant depressive symptoms in people with extremely short prognoses warrant further investigation.

In contrast, when exploring the prevalence of depressive symptoms using diagnostic criteria (gold-standard) for specific depressive disorders, the prevalence of major and minor depression represented a relative minority. Major and minor depressions accounted for only 10% and 5% respectively of those with extremely short prognoses and clinically significant depressive symptoms. This reflects the observations that clinically significant mood disturbances are prevalent (around 40%) but major depression is relatively uncommon in the general cancer or terminal settings.[89,92] In fact, the prevalence of major depression and other associated mental disorders might not increase as death approaches.[92] Nonetheless, the pooled prevalence of combined depressive disorders (major and minor depression, dysthymia and mood disorders due to general medical conditions with depressive features) found in this review was high, at 47% by Zhao et al..[48] This raises the possibility that much of the clinically significantly depressed individuals with extremely short prognoses may not be diagnosed with major or minor depression, but rather, be labeled as other disorders with depressive features (e.g., adjustment disorder).[84] Interestingly, the composite prevalence of various depressive disorders for people with extremely short prognoses of 47% seemed to equate to the prevalence of depressive symptoms defined using screening tools (as seen in the results of the low-risk-of-bias studies and the pooled prevalence of 50%−55% in meta-analyses using tools).[48,49] This raises the possibility that, in those with extremely short prognoses, one can use depression screening tools such as HADS or PHQ to estimate the combined prevalence of various depressive disorders (and therefore the burden of depression). This would avoid the need to undergo extensive psychiatric interviews as required by the diagnostic criteria for patients for whom these interviews might be too burdensome and thus not be feasible. This too warrants future study. In contrast, for diagnostic purposes, these screening tools should not replace diagnostic criteria in diagnosing depressive disorders.[63] Rather, these screening tools are means to help clinicians identify individuals with clinically significant symptoms needing interventions.

Limitations: Quality Assessment/Risk-of-Bias

The predominant types of risk of bias across studies in this review, consistent with the other similar systematic reviews exploring the prevalence of depressive symptoms in advanced life-limiting illnesses, were selection and attrition (nonresponder) biases.[11,12] The findings of this review need to be interpreted considering these biases. In the included studies, a significant proportion of participants with extremely short prognoses were excluded because of their being significantly cognitively impaired or too frail to undergo

study assessment (even up to 75% in one study).[47] Given the assessment of depressive disorder is contentious for those with significant cognitive impairment or dementia, marked by a wide range of prevalence of depressive symptoms, prevalence studies in the setting of significant cognitive impairment or dementia were excluded in this systematic review.[93–95] More than half of the full texts screened (57%) could not have data for those with extremely short prognoses extracted with a lack of the functional status or survival data of interests. There is, therefore, a need for future research involving advanced life-limiting illnesses to include prognostic or survival measures such as those used in this review. Feasible alternative methods of assessing for depressive symptoms in this context also need further investigation.

Another limitation of this review is that studies that used general symptom measurement scales with nonspecific depression measurement such as the Edmonton Symptom Assessment System Depression Score (ESAS) were excluded.[19,21] This was to ensure measurement accuracy. However, prevalence of depressive symptoms in people with extremely short prognoses captured by ESAS in Seow et al., (36%) and Liu et al., (41.7%) was consistent with results of this systematic review.[19,21] This raises the possibility that ESAS may be a feasible screening tool for depressive symptoms in people with extremely short prognoses.

Similar to other systematic reviews reporting prevalence of depressive symptoms in palliative care, this systematic review is limited by the high heterogeneity of the included studies.[11,12] Due to the small number of studies included ($n = 13$) and many studies having a combination of variables (e.g., a combination of malignant and nonmalignant diseases or mixed recruitment settings), extensive investigation of potential moderators that account for heterogeneity using meta-regression cannot be performed with statistical validity. Nonetheless, one can postulates that the majority of heterogeneity is contributed by the same factors listed in other similar systematic reviews: the various populations studied, assessment methods, and depression definitions.[11,12]

Strengths and Other Limitations

First, the results reported by this review represents possibly the largest number of people with extremely short prognoses ($N = 1245$) in the current literature. This review used inclusive search strategies to include the broader population of advance life-limiting illnesses that would not necessarily have been referred to palliative care, as well as both malignant and nonmalignant disease. However, there is a relative lack of representation of studies focusing on nonmalignant disease. This is because many screened nonmalignant studies did not include a measure of functional status, especially later in people's disease trajectory. In addition, there was a lack of studies that reported the prevalence findings of malignant or nonmalignant diseases separately. Therefore, comparison of prevalence estimates between studies with malignant versus nonmalignant disease has not been possible.

An important limitation of this review is the inclusion of studies with small sample sizes into the meta-analysis, introducing the risk of small study effects and publication bias.[96–98] Nonetheless, inverted funnel plots and Egger's regression tests have demonstrated the lack of small study effects. The removal of studies with sample sizes of 100 or less from meta-analyses has demonstrated comparable findings.[96] Perhaps, in this context, a robust estimation of prevalence would be achieved through including all available evidence, as limiting studies due to small study size may introduce subjectivity to the final result.[98] However, the lack of sample size in individual studies have contributed to the overall limited precision of the prevalence estimates. This is indicated by the wide confidence intervals of the prevalence data.

The strength of this review is that the prevalence of clinically significant depressive symptoms has been explored by considering various methods of detection (using depression-specific screening tools and different diagnostic criteria through psychiatric interview). This ensures that the pooled prevalence better reflects the overall global burden of depressive symptoms experienced by this subpopulation.

Another major strength of this study is that this is one of the few reviews with meta-analysis of prevalence that use formal guideline to critically appraise individual studies (JBI Systematic Reviews Checklist for Prevalence Studies) and across studies (GRADE approach), for the first guideline established to appraise individual prevalence studies was only published in 2017.[37–40] For quality assessment across studies, GRADE approach has been frequently used for meta-analysis of cause-and-effect and diagnostic tools.[40,58,99] However, it has yet to be adapted for the use of assessing prevalence studies.[59] Therefore, this systematic review has used the general principles of the GRADE approach to perform quality assessment across studies. The overall GRADE score has not been generated in this review to allow the opportunity for objective judgments by the readers.

Implications

The findings of the increase in prevalence as death approaches with up to half of the people with extremely short prognoses having clinically significant depressive symptoms have major implications for

clinical practice, policymakers and funders, and future research.

Implication for Clinical Practice

There is a need for some forms of systematic processes (e.g., screening for depressed mood on first contact with palliative care services) to increase clinicians' awareness of potentially depressed individuals, as the affected individuals might be reluctant to report symptoms of depression caused by social stigma.[3,11,20] Patients and families may need to be encouraged to talk about their mood by clinicians, and certain components of the depression screening tools might be helpful to act as prompts (e.g., using PHQ-9 to ask about anhedonia).

Emphasis must be placed on clinicians to not neglect patients' concerns of depressed mood in the context of having extremely short prognoses as "normal reactions" to the dying process. Clinicians need to be aware that there is a high likelihood of these patients suffering from depressive symptoms that significantly impair their quality-of-life without meeting the diagnostic criteria of various depressive disorders (subsyndromal depression). The disclosures of these symptoms from patients, therefore, need to be thoroughly explored and addressed, with the expression of depressive symptoms encouraged and destigmatized.[3] Individuals with subsyndromal depression may still benefit from various psychological support interventions to prevent more severe depressive symptoms and disorders from developing.[63] In fact, given the high prevalence of these symptoms, there is an argument that all patients with extremely short prognoses should be offered empathic nonpharmacological supportive services (e.g., counseling/supportive psychotherapy) as primary prevention for possible depressive symptoms, and have the escalation of treatments as deemed appropriate.

Implication for Policymakers and Funders

The high prevalence of clinically significant depressive symptoms in this subgroup of extremely short prognoses necessitate the treating clinicians to be trained and empowered for timely assessment and management of depressive symptoms. The clinical culture needs to be one that offers supportive environment to staffs engaging with depressed patients (e.g., allowing extra time in clinic for depression assessment and offering debriefing sessions for staffs). Integration between palliative care and psychiatry may improve the tendency of under-recognition of depressive symptoms, leading to better depression care.[100–102] Public health interventions aiming at improving public awareness of mood health at the end-of-life, destigmatizing depressive symptoms and encouraging open discussion are also required.[3]

Implication for Future Research

This review highlights the needs for further research in people with advanced life-limiting illnesses and extremely short prognoses as studies focusing on this subpopulation as their primary objectives are lacking. The wide confidence intervals of prevalence estimates found in this study reflects the lack of any agreed nation or international criteria for referral to hospice/palliative care services, and the relatively poor estimation of people's prognosis by many clinicians.[10] Importantly, this systematic review and meta-analysis forms an important first step to create a platform for more uniform population eligibility definitions for future, larger studies. The validity and acceptability of using functional scores as prognostic indicators for extremely short prognosis in nonmalignant diseases need to be further explored.

For depression research in this subpopulation, more prospective longitudinal studies are required to estimate the new occurrences of depressive symptoms better in individuals with extremely short prognoses. Identifying a feasible and acceptable screening tool and assessing the benefits of implementing screening are vital. The optimal method of assessing depressive symptoms, accounting for the possibility of patients not fulfilling certain components of the conventional diagnostic criteria due to the short life expectancy, and the feasibility and acceptability of the substitute approach of diagnosis (i.e., Endicott Criteria) need further exploration.[103] Clinicians' perspectives on assessing and managing depression in this context, as well as the corresponding views from patient and their families also require study.

Conclusion

Clinically significant depressive symptoms (including subsyndromal depression) are common in people with advanced life-limiting illnesses and extremely short prognoses (approximately 50%).

Clinicians caring for people with extremely short prognoses need to be proactive in the recognition and assessment of these symptoms to allow for timely interventions. Much research is required to establish effective assessment and management strategies in this field.

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Appendix

Search Strategy (27th of Feb 2019):

Search strategy in Ovid MEDLINE with the overall framework of: [Palliative Care or Advanced Life-Limiting Illnesses] AND [Prevalence] AND [Depression], limiting to the January 1994 - February 2019 (items 65—66) (search terms were adapted for other electronic databases according to this MEDLINE search strategy):

1. Palliative Care domain (items 1—44):
   - Conventional "Palliative Care" search terms (i.e., Palliative Care, terminally ill, end-of-life) (items 1, 3—5, 40)
   - Additional search terms using various advanced life-limiting illnesses by diseases AND [settings of death or association with mortality] to include population not known to the palliative care services but has advanced life-limiting illnesses and palliative care needs (e.g., [End-stage renal disease AND home death] or [Advanced cancer AND mortality]) (items 2, 6—39, 41—43)
   - Combination of the two above (item 44)
2. Prevalence domain:
   - Studies that include prevalence data (items 45—47)
3. Depression domain:
   - Various depressive disorders/syndromes (items 48—64)

1. PALLIATIVE CARE/or palliative.mp.
2. end-stage.mp.
3. Terminally Ill/or Terminal* ill*.mp.
4. ((end-of-life or death) and dying).mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5. Terminal Care/or terminal care.mp. or Hospice Care/or hospice care.mp.
6. advanced cirrhosis.mp. or Liver Failure/or liver failure.mp. or hepatic failure.mp.
7. renal failure.mp.
8. Kidney Failure, Acute/or Kidney Failure, Chronic/or stage 5 chronic kidney disease.mp. or stage V chronic kidney disease.mp.
9. pulmonary failure.mp.
10. respiratory failure.mp. or respiratory failure/
11. heart failure.mp. or Heart Failure/or cardiac failure.mp.
12. advanced multiple sclerosis.mp.
13. advanced dementia.mp.
14. Neurodegenerative Diseases/or neurodegenerat*.mp.
15. Motor Neuron Disease/or Amyotrophic Lateral Sclerosis/or motorneuron disease*.mp. or motor neurone disease*.mp. or motorneurone disease*.mp. or motor neuron disease*.mp. or Muscular Atrophy, Spinal/or spinal muscular atrophy.mp.
16. Acquired immune deficiency syndrome.mp. or Acquired Immunodeficiency Syndrome/
17. AIDS.mp.
18. multiple organ failure.mp. or Multiple Organ Failure/
19. (multiorgan failure or multi organ failure).mp.
20. advanced cancer.mp.
21. terminal cancer.mp.
22. metastatic cancer.mp.
23. stage 4 cancer.mp.
24. stage IV cancer.mp.
25. geriatric*.mp. or GERIATRIC ASSESSMENT/or GERIATRIC PSYCHIATRY/
26. Critical Care/
27. early goal-directed therapy/or early goal-directed therapy.mp.
28. (critical care or intensive care).mp.
29. hospice*.mp. or Hospices/
30. INPATIENTS/or inpatient*.mp
31. hospitali#ation.mp. or Hospitalization/
32. Nursing Homes/or Homes for the Aged/or nursing home*.mp.
33. Neoplasms/
34. home death.mp.
35. group home*.mp. or Group Homes/
36. care home*.mp.
37. Parkinson disease.mp. or Parkinson Disease/
38. MORTALITY/
39. fatal outcome.mp. or Fatal Outcome/
40. 1 or 3 or 4 or 5

Annotation: Part 1: pall care component nature - traditional pall care.

41. 2 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 33 or 37

Annotation: Pall care diseases.

42. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 34 or 35 or 36 or 38 or 39

Annotation: pall care components (setting/death)

43. 41 and 42

Annotation: Part 2: pall care (life threatening diseases AND setting/death)

44. 40 or 43

Annotation: Total Pall care (Part 1 traditional pall care nature + Part 2 life threatening diseases AND setting/death)

45. PREVALENCE/or prevalence.mp.

46. Cross-Sectional Studies/

47. 45 or 46

48. Adjustment Disorders/or adjustment disorder*.mp.

49. Grief/or complicated grief.mp.

50. sadness.mp.

51. demorali*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

52. hopeless*.mp.

53. BIPOLAR DISORDER/or bipolar.mp.

54. Psychotic Disorders/or schizoaffective.mp.

55. persistent depressive disorder.mp.

56. Dysthymic Disorder/or dysthymi*.mp.

57. DEPRESSION/

58. depressive disorder.mp. or Depressive Disorder/

59. depress*.mp.

60. 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59

61. *Heart Rate/

62. *Blood Pressure/

63. 61 or 62

64. 60 not 63

65. 44 and 47 and 64

Annotation: pall care + prevalence + depression.

66. limit 65 to last 25 years

Appendix 2. Prevalence Systematic Review Search Strategy

Search Strategy for the Systematic Review – Prevalence Studies (27th of Feb 2019):

Search strategy in Ovid MEDLINE with the overall framework of: [Palliative Care or Advanced Life-Limiting Illnesses] AND [Prevalence] AND [Depression], limiting to the January 1994 - February 2019 (items 65-66) (search terms were adapted for other electronic databases according to this MEDLINE search strategy):

1. Palliative Care domain (Items 1-44):
    - Conventional "Palliative Care" search terms (i.e. Palliative Care, terminally ill, end-of-life) (Items 1, 3-5, 40)
    - Additional search terms using various advanced life-limiting illnesses by diseases AND [settings of death or association with mortality] to include population not known to the palliative care services but has advanced life-limiting illnesses and palliative care needs (e.g. [End-stage renal disease AND home death] or [Advanced cancer AND mortality]) (Items 2, 6-39, 41-43)
    - Combination of the two above (Item 44)
2. Prevalence domain:
    - Studies that include prevalence data (Items 45-47)
3. Depression domain:
    - Various depressive disorders /syndromes (Items 48-64)

---

1 PALLIATIVE CARE/ or palliative.mp.

2 end-stage.mp.

3 Terminally Ill/ or Terminal* ill*.mp.

4 ((end-of-life or death) and dying).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

5 Terminal Care/ or terminal care.mp. or Hospice Care/ or hospice care.mp.

6 advanced cirrhosis.mp. or Liver Failure/ or liver failure.mp. or hepatic failure.mp.

7 renal failure.mp.

8 Kidney Failure, Acute/ or Kidney Failure, Chronic/ or stage 5 chronic kidney disease.mp. or stage V chronic kidney disease.mp.

9 pulmonary failure.mp.

10 respiratory failure.mp. or respiratory failure/

11 heart failure.mp. or Heart Failure/ or cardiac failure.mp.

12 advanced multiple sclerosis.mp.

13 advanced dementia.mp.

14 Neurodegenerative Diseases/ or neurodegenerat*.mp.

15 Motor Neuron Disease/ or Amyotrophic Lateral Sclerosis/ or motorneuron disease*.mp. or motor neurone disease*.mp. or motorneurone disease*.mp. or motor neuron disease*.mp. or Muscular Atrophy, Spinal/ or spinal muscular atrophy.mp.

16 Acquired immune deficiency syndrome.mp. or Acquired Immunodeficiency Syndrome/

17 AIDS.mp.

18 multiple organ failure.mp. or Multiple Organ Failure/

19 (multiorgan failure or multi organ failure).mp.

20 advanced cancer.mp.

21 terminal cancer.mp.

22 metastatic cancer.mp.

23 stage 4 cancer.mp.

24 stage IV cancer.mp.

25 geriatric*.mp. or GERIATRIC ASSESSMENT/ or GERIATRIC PSYCHIATRY/

26 Critical Care/

27 early goal-directed therapy/ or early goal-directed therapy.mp.

28 (critical care or intensive care).mp.

29 hospice*.mp. or Hospices/

30 INPATIENTS/ or inpatient*.mp

31 hospitali#ation.mp. or Hospitalization/

32 Nursing Homes/ or Homes for the Aged/ or nursing home*.mp.

33 Neoplasms/

34 home death.mp.

35 group home*.mp. or Group Homes/

36 care home*.mp.

37 Parkinson disease.mp. or Parkinson Disease/

38 MORTALITY/

39 fatal outcome.mp. or Fatal Outcome/

40 1 or 3 or 4 or 5

Annotation: Part 1: pall care component nature - traditional pall care

41 2 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 33 or 37

Annotation: Pall care diseases

42 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 34 or 35 or 36 or 38 or 39

Annotation: pall care components (setting / death)

43 41 and 42

Annotation: Part 2: pall care (life threatening diseases AND setting/death)

44 40 or 43

Annotation: Total Pall care (Part 1 traditional pall care nature + Part 2 life threatening diseases AND setting/death)

45 PREVALENCE/ or prevalence.mp.

46 Cross-Sectional Studies/

47 45 or 46

48 Adjustment Disorders/ or adjustment disorder*.mp.

49 Grief/ or complicated grief.mp.

50 sadness.mp.

51 demorali*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

52 hopeless*.mp.

53 BIPOLAR DISORDER/ or bipolar.mp.

54 Psychotic Disorders/ or schizoaffective.mp.

55 persistent depressive disorder.mp.

56 Dysthymic Disorder/ or dysthymi*.mp.

57 DEPRESSION/

58 depressive disorder.mp. or Depressive Disorder/

59 depress*.mp.

60 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59

61 *Heart Rate/

62 *Blood Pressure/

63 61 or 62

64 60 not 63

65 44 and 47 and 64

Annotation: pall care + prevalence + depression

66 limit 65 to last 25 years

Appendix 3. Joanna Briggs Institute Systematic Review Checklist for Prevalence Studies

Joanna Briggs Institute Systematic Review Checklist for Prevalence Studies Items 1-9 (Options: 'Yes'; 'No'; 'Unclear'; and 'Not Applicable'):

1. Was the sample frame appropriate to address the target population?
2. Were study participants sampled in an appropriate way?
3. Was the sample size adequate?
4. Were the study subjects and the setting described in detail?
5. Was the data analysis conducted with sufficient coverage of the identified sample?
6. Were valid methods used for the identification of the condition?
7. Was the condition measured in a standard, reliable way for all participants?
8. Was there appropriate statistical analysis?
9. Was the response rate adequate, and if not, was the low response rate managed appropriately?

Overall appraisal: Include; Exclude; Seek further info (All 13 studies were included)

Appendix 4. Systematic Review of Effective Interventions

JOURNAL OF PALLIATIVE MEDICINE
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Letters to the Editor

Evidence of Effective Interventions for Clinically Significant Depressive Symptoms in Individuals with Extremely Short Prognoses Is Lacking: A Systematic Review

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Dear Editor:

Clinically significant depressive symptoms are prevalent in people with advanced life-limiting illnesses and extremely short prognoses (i.e., days to weeks).[1] Nonetheless, management can be challenging due to insufficient time for intervention effects, while co-existing symptom burdens (e.g., fatigue and dysphagia) and organ dysfunctions limit intervention tolerability.[2,3] Currently, systematic review evidence for depression interventions in the specific setting of extremely short prognoses is lacking.

We conducted a systematic review to determine what interventions were effective for clinically significant depressive symptoms in people with advanced life-limiting illnesses and extremely short prognoses (PROSPERO registration: CRD42019125119). We searched for randomized controlled trials (RCTs) of nonpharmacological and pharmacological interventions (January 1994–June 2021) using MEDLINE (OVID), PsycINFO, Embase, CINAHL, and CareSearch. Inclusion criteria for studies were ≥18 years old with advanced life-limiting illnesses, extremely short prognoses (absolute survival <2 months or a functional status indicative of ≤4 weeks median survival [e.g., Karnofsky Performance Status ≤40 or Eastern Cooperative Oncology Group Grade 4]), and clinically significant depressive symptoms, defined by a validated depression-specific tool or diagnostic criteria (e.g., Diagnostic Statistical Manual). We excluded studies that were not English language, peer-reviewed, RCT, and studies without clinically significant depressive symptoms in the inclusion criteria for randomization or pre- and post-intervention depression outcome measures. We hand-searched reference lists of systematic reviews and contacted authors for full texts and data. Quality assessment was planned using the Scottish Intercollegiate Guidelines Network Methodology Checklists for controlled trials for individual studies, and Grading of Recommendations Assessment, Development and Evaluation across studies.

Of 6107 screened articles, none met the eligibility criteria (Fig. 1). The primary reason for RCT full-text exclusion related to target population issues ($n = 100$; 41.3%): 55 did not include extractable data for the subgroup with extremely short prognoses; 11 did not have depressive symptoms in their inclusion criteria during randomization; 33 were excluded due to both reasons; and 1 due to the contentious nature of diagnosing depressive disorder in the dementia population.

Our review demonstrates that clinicians do not currently have RCT data to inform the use of any nonpharmacological or pharmacological interventions for depression in patients with extremely short prognoses. Consequently, when considering interventions for depressive symptoms for people in the last days to weeks of life, clinicians should exercise caution when extrapolating data from the broader literature and carefully assess potential benefits and harms after initiating any therapy.[4]

Researchers in this field need to consider including and explicitly identifying people with extremely short prognoses and clinically significant depressive symptoms using validated methods before randomization in their studies. To

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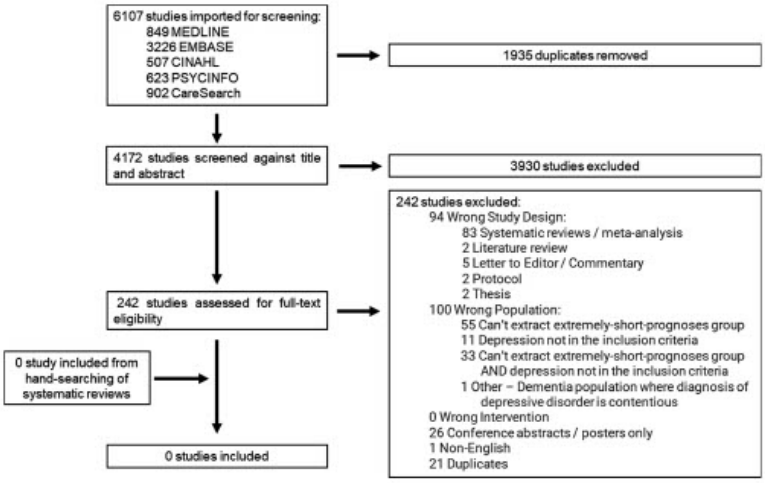

FIG. 1. PRISMA flow diagram. Out of 6107 studies identified and 242 studies assessed for full-text eligibility, no study was identified as eligible for analysis.

improve the feasibility of generating evidence for this group, researchers may consider alternative trial designs (e.g., n-of-1 or Bayesian response-adaptive randomization). Non-RCT designs can also be considered, using death or set levels of functional status as anchor points, following participants prospectively until death.

Overall, this review highlights the evidence gap for interventions for clinically significant depressive symptoms in the extremely short prognosis setting, and the implications for clinicians and researchers striving to optimize depression care at the end of life.

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4. Currow DC: Why don't we do more rigorous clinical research so that we can stop experimenting on patients? J Palliat Med 2010;13:636–637.

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Appendix 5. Effective Intervention Systematic Review Search Strategy

Search Strategy for the Systematic Review – Intervention Studies (11th of Mar 2020):

Search strategy in Ovid MEDLINE with the overall framework of: [Palliative Care or Advanced Life-Limiting Illnesses] AND [Depression] AND [Randomised Controlled Trial], limiting to the January 1994 – March 2020 (items 65-66) (search terms were adapted for other electronic databases according to this MEDLINE search strategy):

1. PALLIATIVE CARE/ or palliative.mp.

2. end-stage.mp.

3. Terminally Ill/ or Terminal* ill*.mp.

4. ((end-of-life or death) and dying).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

5. Terminal Care/ or terminal care.mp. or Hospice Care/ or hospice care.mp.

6. advanced cirrhosis.mp. or Liver Failure/ or liver failure.mp. or hepatic failure.mp.

7. renal failure.mp.

8. Kidney Failure, Acute/ or Kidney Failure, Chronic/ or stage 5 chronic kidney disease.mp. or stage V chronic kidney disease.mp.

9. pulmonary failure.mp.

10. respiratory failure.mp. or respiratory failure/

11. heart failure.mp. or Heart Failure/ or cardiac failure.mp.

12. advanced multiple sclerosis.mp.

13. advanced dementia.mp.

14. Neurodegenerative Diseases/ or neurodegenerat*.mp.

15. Motor Neuron Disease/ or Amyotrophic Lateral Sclerosis/ or motorneuron disease*.mp. or motor neurone disease*.mp. or motorneurone disease*.mp. or motor neuron disease*.mp. or Muscular Atrophy, Spinal/ or spinal muscular atrophy.mp.

16. Acquired immune deficiency syndrome.mp. or Acquired Immunodeficiency Syndrome/

17. AIDS.mp.

18. multiple organ failure.mp. or Multiple Organ Failure/

19. (multiorgan failure or multi organ failure).mp.

20. advanced cancer.mp.

21. terminal cancer.mp.

22. metastatic cancer.mp.

23. stage 4 cancer.mp.

24. stage IV cancer.mp.

25. geriatric*.mp. or GERIATRIC ASSESSMENT/ or GERIATRIC PSYCHIATRY/

26. Critical Care/

27. early goal-directed therapy/ or early goal-directed therapy.mp.

28. (critical care or intensive care).mp.

29. hospice*.mp. or Hospices/

30. INPATIENTS/ or inpatient*.mp.

31. hospitali#ation.mp. or Hospitalization/

32. Nursing Homes/ or Homes for the Aged/ or nursing home*.mp.

33. Neoplasms/

34. home death.mp.

35. group home*.mp. or Group Homes/

36. care home*.mp.

37. Parkinson disease.mp. or Parkinson Disease/

38. MORTALITY/

39. fatal outcome.mp. or Fatal Outcome/

40. 1 or 3 or 4 or 5

41. 2 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 33 or 37

42. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 34 or 35 or 36 or 38 or 39

43. 41 and 42

44. 40 or 43

45. Adjustment Disorders/ or adjustment disorder*.mp.

46. Grief/ or complicated grief.mp.

47. sadness.mp.

48. demorali*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

49. hopeless*.mp.

50. BIPOLAR DISORDER/ or bipolar.mp.

51. Psychotic Disorders/ or schizoaffective.mp.

52. persistent depressive disorder.mp.

53. Dysthymic Disorder/ or dysthymi*.mp.

54. DEPRESSION/

55. depressive disorder.mp. or Depressive Disorder/

56. depress*.mp.

57. 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56

58. *Heart Rate/

59. *Blood Pressure/

60. 58 or 59

61. 57 not 60

62. Meta-Analysis as Topic/ or meta-analysis.mp. or meta analysis.mp.

63. (randomi#ed control* trial* or randomi#ed clinical trial*).mp.

64. Randomised Controlled Trial/

65. systematic review*.mp.

66. 62 or 63 or 64 or 65

67. 44 and 61 and 66

68. limit 67 to last 26 years

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Appendix 6. Survey of Palliative Physician (BMC Palliative Care)

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https://doi.org/10.1186/s12904-022-00901-y

BMC Palliative Care

RESEARCH Open Access

Caring for depression in the dying is complex and challenging – survey of palliative physicians

Wei Lee[1,2*], Sungwon Chang[1], Michelle DiGiacomo[1], Brian Draper[3], Meera R. Agar[1] and David C. Currow[4]

Abstract

Background: Depression is prevalent in people with very poor prognoses (days to weeks). Clinical practices and perceptions of palliative physicians towards depression care have not been characterised in this setting. The objective of this study was to characterise current palliative clinicians' reported practices and perceptions in depression screening, assessment and management in the very poor prognosis setting.

Methods: In this cross-sectional cohort study, 72 palliative physicians and 32 psychiatrists were recruited from Australian and New Zealand Society of Palliative Medicine and Royal Australian and New Zealand College of Psychiatrists between February and July 2020 using a 23-item anonymous online survey.

Results: Only palliative physicians results were reported due to poor psychiatry representation. Palliative physicians perceived depression care in this setting to be complex and challenging. 40.0% reported screening for depression. All experienced uncertainty when assessing depression aetiology. Approaches to somatic symptom assessment varied. Physicians were generally less likely to intervene for depression than in the better prognosis setting. Most reported barriers to care included the perceived lack of rapidly effective therapeutic options (77.3%), concerns of patient burden and intolerance (71.2%), and the complexity in diagnostic differentiation (53.0%). 66.7% desired better collaboration between palliative care and psychiatry.

Conclusions: Palliative physicians perceived depression care in patients with very poor prognoses to be complex and challenging. The lack of screening, variations in assessment approaches, and the reduced likelihood of intervening in comparison to the better prognosis setting necessitate better collaboration between palliative care and psychiatry in service delivery, training and research.

Keywords: Depression, Palliative care, Psychiatry, Terminal care, Prognosis, Surveys and questionnaires

Background

Depression is a distressing condition for people with advanced life-limiting illnesses. It can reduce the quality-of-life of those affected and others around them, exacerbate physical suffering and worsen psycho-existential distresses [1–4]. Not only does depression impact patient engagement with their nearest supporters, but depression can also negatively affect clinicians' ability to deliver care [1, 5]. Despite its prevalence, there is evidence that depression has been under-assessed and, even when recognised, under-managed in the palliative care setting [6–9].

In the palliative care population, there is a sub-group of patients with very poor prognoses defined as an estimated life expectancy in the range of days to weeks. This sub-group is characterised by a high degree of frailty,

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often with significant symptom burden and rapidly declining functional status [10, 11]. The frailty, symptom burden (e.g. fatigue, confusion, and dysphagia), and limited time for interventions to take effect can make depression assessment, psychotherapies and administration of typical antidepressants (e.g. Selective Serotonin Reuptake Inhibitors [SSRIs] and Serotonin Noradrenaline Reuptake Inhibitors [SNRIs]) challenging for clinicians [12–14]. Subsequently, clinicians' approaches to depression assessment and management for these people might differ from palliative patients with better prognoses.

While previous studies of clinicians' approaches to depression assessment and management in the general palliative care population have been done in Australia and the United Kingdom, palliative physicians' and psychiatrists' approaches to depression care specifically for people with very poor prognoses have not been explored [8, 9, 15].

Methods

Aim

This study aimed to characterise current Australasian palliative clinicians' (palliative physicians and psychiatrists) reported practices and perceptions in depression assessment and management for palliative patients with very poor prognoses, including identifying barriers to optimising depression care in this context.

Study Design

This was a cross-sectional cohort study using an online survey.

Respondents

Eligible respondents were: 1. current members of the Australian and New Zealand Society of Palliative Medicine (ANZSPM), the largest Australasian professional society for medical practitioners interested in palliative medicine, including specialist physicians (e.g. palliative physicians and renal physicians), general practitioners, and radiation oncologists; and 2. psychiatry fellows and trainees registered with the Royal Australian and New Zealand College of Psychiatrists (RANZCP).

Survey

The anonymous online survey (Additional file 1) used the Research Electronic Data Capture (REDCap) platform. It contained branching logic with a maximum of 23 questions (four multiple response questions and 19 single response questions) for each respondent, tailored according to the respondent's self-identified primary discipline (palliative medicine or psychiatry) and previous encounters with patients with very poor prognoses. It explored the domains of depression screening, assessment, management and integration between psychiatry and palliative care services for patients with very poor prognoses based on extrapolation from the general palliative care literature and investigators' clinical experiences [9, 14, 16, 17]. Particularly, interventions that might produce rapid antidepressant effects in the very poor prognosis setting such as adjunct antipsychotics, psychostimulants, ketamine and electroconvulsive therapy (ECT) were explored [18–21]. The survey contained two opened-ended questions asking for perceived challenges or barriers to effective assessment and management of depression in patients with very poor prognoses. To increase feasibility, validity and reliability, the survey questions were developed by the investigator panels consisting of clinical academic experts from palliative care and psychiatry and piloted with four palliative physicians without needing to further modify the questionnaire. The survey took, on average, 8 minutes to complete, on piloting.

Recruitment

The survey link was first distributed by the professional bodies to members on the 25th of Feb 2020 (ANZSPM) and the 1st of May 2020 (RANZCP). Due to the restrictions of the survey dissemination policies, capacity for sending reminder emails was limited: for ANZSPM, only one reminder email was sent after 2 weeks; for RANZCP, no reminder email could be sent to the entire cohort but one reminder email was sent to the College Faculty of Consultation Liaison, after 6 weeks (12th of June 2020). Apart from the RANZCP mass cohort distribution, where the survey link was distributed as part of an electronic newsletter (Psyche), survey links were contained within the email distributed by the professional bodies (ANZSPM and RANZCP College Faculty of Consultation Liaison). The survey was closed on the 31st of Jul 2020. No financial incentives were offered to respondents.

Data Analysis

Quantitative data were expressed as the number of respondents (percentage) and analysed using a IBM SPSS Statistics 26 [22].

Responses to the two open-ended items were analysed independently by two investigators (WL and MD) using conventional qualitative content analysis, which aligns with the aims of this study [23, 24]. WL was a palliative care physician who has clinical experience as a psychiatry resident, and MD was an experienced qualitative health researcher. Codes were developed inductively through careful reading of the data and sorted into categories of related material in NVivo 12. Categories were refined, defined, and subcategories developed through analyst discussion until consensus was achieved [23, 24].

Quantification of responses within subcategories was performed using NVivo 12 [25].

Results

Completed surveys were obtained from 110 individuals: 79 responses out of 522 members of ANZSPM (15.1%); and 31 out of 6655 RANZCP members (0.5%). Of the 110 responses, 72 respondents identified as having the primary specialty of palliative medicine and 32 with psychiatry. Due to the lack of response from the RANZCP members and hence the lack of representation of the Australasian psychiatry cohort, only results from those who identified themselves primarily as palliative physicians ($n=72$) were reported (Table 1).

Participating clinicians were mainly specialist and fellows (73.6%); female (75.0%); aged 31–60-year-old (87.4%); primarily working in Australia (76.4%); graduated more than 10 years ago (88.9%); and working ≥20 clinical hours per week (90.2%). Most clinicians ($n=70$; 97.2%) reported having encountered depression in people with very poor prognoses.

The majority ($n=42$; 58.3%) of all palliative physicians reported that they screen for depression in general palliative care patients, while only 40.0% ($n=28$ out of 70) of clinicians encountering patients with very poor prognoses reported screening for depression.

Among physicians who might screen for depression (answered "yes" or "depends") in general palliative care patients, the primary screening method reported was clinical interview ($n=53$; 93.0%), followed by asking the family/carers ($n=40$; 70.2%), asking other health professionals involved in the care ($n=37$; 64.9%), and the use of screening tools ($n=27$; 47.4%). For the very poor prognoses group, while 68.6% ($n=48$) of physicians reported no difference in the way of screening compared to the general palliative population, 18.6% ($n=13$) reported a "difference": taking a more reactive rather than proactive approach; being briefer in assessment; relying more on objective information sources; and emphasising less on somatic symptoms. Among those who reported to use screening tools (n=27), the most commonly used tools was the ultra-short two-items questionnaire ($n=14$; 51.8%) followed by a single-item questionnaire (n=5; 18.5%) (e.g. asking "Are you depressed" and/or "Have you had little interest or pleasure in doing things"). Only one respondent reported to use Hospital Anxiety and Depression Scale.

For depression assessment, at least 80% of physicians would ascertain whether the depression episode is first or recurrent during assessment, regardless of whether the prognoses is very poor or not. All physicians who have encountered depressed patients with very poor prognoses have experienced uncertainty regarding the cause of depression. Most palliative physicians ($n=56$; 80.0%) would treat the depressed mood despite the uncertain cause. The primary sources of assistance sought by palliative physicians in this context were from psychiatry ($n=33$; 47.1%) and psychology ($n=29$; 41.4%).

For depression somatic symptom assessment, the majority (n=37; 51.4%) of physicians reported including somatic symptoms in the general palliative care patients while excluding somatic symptoms in the sub-group with very poor prognoses (n=29; 41.4%). Notably, in the setting of very poor prognoses, 30.0% ($n=21$) of physicians reported "depends": whether the somatic symptoms could be attributable to the nature of the terminal illnesses and associated interventions on an individual basis; and that somatic symptoms were still valuable to be considered in the "overall picture" of the patient.

For various treatment approaches for major depressive disorder in the setting of very poor prognoses (Table 2), most physicians reported using non-pharmacological approaches ($n=64$; 91.4%), followed by the use of typical antidepressants ($n=63$; 90%). When comparing the likelihood of using various depression interventions in the very poor prognoses sub-group as compared to the general palliative care cohort, the majority of physicians reported: no difference or less likely in using non-pharmacological interventions (both groups: $n=26$; 37.1%), and less likely to use typical antidepressants ($n=36$; 51.4%). For ECT in the setting of very poor prognosis, 72.9% ($n=51$) and 14.3% ($n=10$) of physicians reported to not use or less likely to use it respectively. There were bimodal distributions with the highest prevalence of "I don't use" followed by "more likely to use" for treatment options of: atypical antipsychotics (n=26; 37.1% - "I don't use" and $n=20$; 28.6% - "more likely"); benzodiazepines (n=28; 40.0% - "I don't use" and $n=24$; 34.3% - "more likely"); and novel medication/experimental trials ($n=49$; 70% - "I don't use" and $n=12$; 17.1% - "more likely"). Due to technical issues in the online survey platform, the psychostimulant item was initially not available for the first 28 participants, leading to the large proportion of non-response (n=27; 38.6%) for this item. Despite this limitation, among the responders, the majorities answered "I don't use" or "more likely to use" (both groups $n=18$ out of 43; 41.9%).

For service linkage with psychiatry (Table 3), the majority of palliative physicians reported to request for psychiatry input in an interval of monthly or longer ($n=41$; 56.9%) and being requested by psychiatry for palliative care input yearly or longer (n=26; 36.1%). Two-thirds of the palliative physicians (n=48) thought contract frequency with psychiatry should be more frequent.

Sixty-six respondents (91.7%) provided answers to the open-ended questions regarding key challenges or barriers to effective assessment and management of depression in palliative care patients with

Table 1 Demographics of Respondents

	Palliative Physicians ($n = 72$) [n/%]
Position	
Specialist & Fellow	53 (73.6%)
Trainee	16 (22.2%)
Other	3 (4.2%)
Training Background Apart From Palliative Medicine	42 (58.3%)
GP	25 (34.7%)
Other Physician Training	13 (18.1%)
Critical Care (Emergency, Intensive Care, Anaesthetics)	1 (1.4%)
Psychiatry	1 (1.4%)
Other[a]	7 (9.7%)
Gender	
Male	18 (25.0%)
Female	54 (75.0%)
Country	
Australia	55 (76.4%)
New Zealand	17 (23.6%)
Years Since Medical Graduation	
< 10 years	8 (11.1%)
10–19 years	27 (37.5%)
20 or more years	37 (51.4%)
Age	
21–30	2 (2.8%)
31–40	20 (34.7%)
41–50	15 (20.8%)
51–60	23 (31.9%)
61–70	7 (9.7%)
71–80	0 (0.0%)
Clinical Hours/ week	
< 10	2 (2.8%)
10–19	5 (6.9%)
20–29	15 (20.8%)
30–39	32 (44.4%)
40 or more	18 (25.0%)
Clinical Roles[b]	
Community (patient home, group home and residential aged care facilities)	35 (48.6%)
Outpatient Clinic	35 (48.6%)
Consultative Service in Acute Hospital	45 (62.5%)
Acute Inpatient (Palliative Care or Psychiatry Wards in Acute Hospital)	28 (38.9%)
Subacute Hospital (Palliative Care Unit / Hospice / Subacute Psychiatry Unit)	30 (41.7%)
Encounter depression in very poor prognoses	70 (97.2%)[c]

[a] Other training backgrounds include Bioethics, Public Health, Pain Medicine, Oncology, Nursing, and General Paediatrics. [b]Respondents could report multiple clinical roles. [c]This number included a palliative medicine respondent ($n = 1$) who answered "Other" when asked about previous encounter of depression in the very poor prognosis setting due to difficulty in distinguishing pathological depressed mood from normal grief

very poor prognoses. Respondents commented on the complexity of the clinical situation with interaction between physical, psychosocial, and spiritual dimensions. Reported key challenges and barriers are listed in Table 4, categorised under the domains of patient, clinician, health system, literature and society. On quantifying the various domain subcategories (Table 4), the three most frequently reported barriers were: the lack of therapeutic options that are rapidly effective (77.3%); the perceived frailty, burden and

Table 2 Clinicians' Approaches to Major Depressive Disorder in People with Very Poor Prognoses Versus Better Prognoses

INTERVENTION	RESPONSE	PALLIATIVE PHYSICIANS *(n = 70)* [counts (%)]
a. Non-pharmacological interventions (e.g. supportive psychotherapy / counselling, cognitive therapy)	I don't use	2 (2.9)
	Less likely (cumulative)	26 (37.1)
	No difference	26 (37.1)
	More likely (cumulative)	12 (17.1)
	No response	4 (5.7)
b. Typical antidepressant	I don't use	3 (4.3)
	Less likely (cumulative)	36 (51.4)
	No difference	18 (25.7)
	More likely (cumulative)	9 (12.9)
	No response	4 (5.7)
c. Psychostimulant (e.g. methylphenidate, modafinil)≠	I don't use	18 (25.7)
	Less likely (cumulative)	3 (4.3)
	No difference	4 (5.7)
	More likely (cumulative)	18 (25.7)
	No response	27 (38.6)
d. Atypical antipsychotics (e.g. risperidone, olanzapine)	I don't use	26 (37.1)
	Less likely (cumulative)	6 (8.6)
	No difference	14 (20)
	More likely (cumulative)	20 (28.6)
	No response	4 (5.7)
e. Benzodiazepine	I don't use	28 (40.0)
	Less likely (cumulative)	2 (2.9)
	No difference	12 (17.1)
	More likely (cumulative)	24 (34.3)
	No response	4 (5.7)
f. Novel medication / experimental trials (e.g. ketamine, esketamine nasal spray)	I don't use	49 (70)
	Less likely (cumulative	4 (5.7)
	No difference	1 (1.4)
	More likely (cumulative)	12 (17.1)
	No response	4 (5.7)
g. Electroconvulsive therapy	I don't use	51 (72.9)
	Less likely (cumulative)	10 (14.3)
	No difference	4 (5.7)
	More likely (cumulative)	1 (1.4)
	No response	4 (5.7)

≠ Due to a technical fault, the survey item exploring psychostimulant use was initially not accessible to the first 28 Australian and New Zealand Society of Palliative Medicine (ANZSPM) respondents

intolerance of depression assessment and management on the patient (71.2%); and the complexity in differentiating the symptoms of terminal illness from the somatic symptoms of depression (53.0%).

Discussion

This is the first study that captures palliative physicians' practices and perceptions regarding depression care specifically in people with very poor prognoses of only days to weeks. As demonstrated by the survey, encountering depression in patients with very poor prognoses was common to palliative physician. However, despite the high prevalence of depression (up to 50%) in this population and the frequency of clinical encounters, only 40% of clinicians reported to screen for depression, with all clinicians reported to have experienced uncertainty when assessing the cause of depression [26]. This is reflected by the current study finding of the perceived challenging

Table 3 Palliative Care and Psychiatry Service Linkage

Palliative Physicians (n = 72)		*Number (%)*
For assessment and management of depression in the overall palliative care setting, on average how often have you asked psychiatry for input?	Never	3 (4.2)
	Yearly or longer	16 (22.2)
	Monthly or longer	41 (56.9)
	Weekly or longer	6 (8.3)
	Daily or longer	0 (0.0)
	No response	6 (8.3)
For patients with depression and palliative care needs, on average how often have you been asked by psychiatry to provide palliative care management advice?	Never	24 (33.3)
	Yearly or longer	26 (36.1)
	Monthly or longer	15 (20.8)
	Weekly or longer	1 (1.4)
	Daily or longer	0 (0.0)
	No response	6 (8.3)
For optimal patient care, do you think contact frequency with psychiatry should be:	More frequent	48 (66.7)
	About right	9 (12.5)
	Other	9 (12.5)
	No response	6 (8.3)

complexity of depression care in the very poor prognosis setting by clinicians. According to the literature, this complexity may be contributed to by the interplay of various domains of challenges reported in Table 4: 1) Patients' frailty, co-existing symptom burden and associated end-of-life issues when time for intervention effects is poor [9, 14]; 2) Clinicians' self-perceived limitations of psychiatry skills in the palliative care setting and incompetence in diagnostic differentiation [9, 27]; 3) Health system's inadequacy of resources and access to required interventions in the local health services (e.g. mental health services) [8, 9]; 4) Heterogeneity of depression concept and the lack of evidence to guide practice in the literature for this context [26, 28]; and 5) Unsupportive societal attitudes that prevents the optimisation of depression care (e.g. stigma of mental illnesses, the "normalisation" or "acceptance" of depression at the end-of-life) [29, 30]. Each of these domains warrant future exploration for potential solutions to better optimise depression care in this setting.

Palliative physicians reported to less likely screen for depression and have ambivalence in depression assessment methods (e.g. approach to somatic symptoms of depression) in the very poor prognosis setting compared to the better prognosis setting. Diagnosing depression in the setting of very poor prognosis can be challenging as the symptoms of terminal illnesses (e.g. fatigue and weight loss) can confound the somatic symptoms of depression [17]. Importantly, this study shows that while clinicians may perceive somatic symptoms of depression to be less useful in depression diagnosis, somatic symptoms are still important to be considered during the overall depression assessment as they can affect the appropriateness of intervention choices. It may be desirable for clinicians to be trained with the various approaches to somatic symptoms such as Endicott Criteria to enable better diagnostic differentiation and depression assessment [31]. While they reported to generally intervene less in this setting (compared to patients with better prognoses), it is worth noting the bimodal distributions of clinicians not-using and more-likely-to-use certain non-typical pharmacological interventions (e.g. psychostimulants, atypical antipsychotics, benzodiazepines and novel medications such as ketamine) that have more augmentation and rapid-onset potentials than typical antidepressants [18–20, 32]. This may reflect clinicians' attitudes where clinicians who were trained and aware of how to leverage the potential benefits of these non-typical treatments while minimising intolerance were more likely to embrace their use. Whereas, clinicians who lacked training or resources for these treatments did not tend to use them. Comparable to the study findings in the United Kingdom primary care and palliative settings, inadequately equipped clinicians may have a nihilistic attitude and ambivalence towards depression screening and assessment [8, 29, 30]. The low reported usage of ECT was likely related to clinicians perceiving the intervention to be overburdensome for people with very poor prognoses [33]. Subsequently, palliative physicians and their multidisciplinary team members should be trained with the necessary skills to screen, assess, and administer first-line

Table 4 Reported Challenges/Barriers to Depression Assessment and Management in People with Very Poor Prognoses

DOMAINS/SUBCATEGORIES	PREVALENCE OF REPORTING OF SUBCATEGORIES AMONG RESPONDENTS (*N* = 66) (%)	EXAMPLE QUOTES
Patient - frailty, co-existing symptom burden and competing priorities of associated end-of-life issues when time for intervention effects is poor		
• Frailty, Burden & Intolerance*	71.2%	• "Fatigue, nausea, pain" (Participant 72) and "declining cognition" (Participant 27) • "Even when good psychology, psychiatry and/or pastoral care are available these patients are often too fatigued to participate in talking therapies" (Participant 25) • "Lack of effective medication which will make a difference without causing unnecessary side effects" (Participant 6)
• Therapeutic Efficacy - Lack of therapeutic options that are rapidly effective in the context of very poor prognoses*	77.3%	• "Time frame required for effect of pharmacologic and non pharmacologic interventions" (Participant 5) • "Timing and the poor prognosis which impedes any intervention to be effective." (Participant 2)
• Competing priorities - Prioritisation of physical or other psychosocial & spiritual co-existing issues, symptoms or goals	21.2%	• "Competing priorities - physical symptoms and planning for end-of-life are often more pressing "(Participant 25) • "Other symptoms take priority and are focused on much more than mood disorders" (Participant 44)
Clinician - self-perceived limitations in psychiatry skills in the palliative care setting with incompetence in diagnostic differentiation		
Challenging diagnostic differentiation		
o Depression vs terminal illness symptoms*	53.0%	• "Challenges differentiating somatic symptoms from depression vs physical illness" (Participant 5) • "Usually hard to teese out how much is depression and how much is part of dying process" (Participant 13)
o Between depressed-mood syndromes or differentials (e.g. existential distress, demoralisation, adjustment disorder, organic brain syndrome)	19.7%	• "Challenges differentiating demoralisation from major depression" (Participant 5) • "Distinguishing between adjustment and depression" (Participant 8) • "Misattribution – e.g. depression with psychotic symptoms being attributed to delirium" (Participant 4)
o Normal vs Pathological	16.7%	• "Hard to distinguish from normal grief" (Participant 19) • "Difficulty assessing the difference between normal reactive mood changes [versus] pathological level of mood changes" (Participant 68)
• Limited Skills & Training	24.2%	• "Limited skills in psychiatric assessment - my last psychiatry placement was as a 3rd year medical student" (Participant 60) • "Limited knowledge of what works to improve mood in limited time frame" (Participant 41)
System – Inadequate health system resources and access to required interventions in the local health services		
• Suboptimal access and delivery of palliative care and mental health services	37.9%	• "High patient numbers for a small number of clinicians; Lack of allied health staff in [palliative care] MDT to deliver interventions" (Participant 31) • "Poor access to psychology/psychiatric services" (Participant 44)
• Lack of access to desired depression interventions	13.6%	• "Lack of access to resources for non-pharmacological management e.g. psychology, music therapy" (Participant 71) • "Access to rapid-acting medications like modafinil" (Participant 42)

Table 4 (continued)

DOMAINS/SUBCATEGORIES	PREVALENCE OF REPORTING OF SUBCATEGORIES AMONG RESPONDENTS (*N* = 66) (%)	EXAMPLE QUOTES
• External Environment	1.5%	• "[Lack of] control of clinical environment" (Participant 31)
• Language & Cultural issues	1.5%	• "Language / cultural barriers" (Participant 64)
Literature - Heterogeneity of depression concept and the lack of evidence to guide practice in the very poor prognosis setting		
• lack of evidence & guidelines	15.2%	• "Uncertainty regarding the best treatment for this population/limited evidence base" (Participant 56)
• Heterogeneity of the concept and definition of depression in very poor prognosis setting	1.5%	• "Lack of defined criteria for diagnosis of depression in this group of patients" (Participant 48)
Society – Unsupportive attitudes and beliefs of patients, family and clinicians that prevents optimisation of depression care		
• Nihilism / Futility	10.6%	• "A sense of futility - Why assess it if there's little I can do about it?"(Participant 25) • "Therapeutic nihilism" (Participant 21)
• Acceptance / Normalisation	12.1%	• "Acceptance that this [depression] is a normal part of end of life" (Participant 21) • "Normalisation" (Participant 40) • "Of course he/she is depressed, he/she is dying" (Participant 4)
• Resistance / Disinclination of patients, public, family or clinicians/staff	4.5%	• "Stigma" (Participant 65) • "Pressure from other health care professionals not to treat patients as they are dying" (Participant 34) • "Family not willing to engage non-pharm [intervention s]" (Participant 64)

*Top three most commonly reported barriers: the lack of therapeutic options that are rapidly effective (77.3%); the perceived frailty, burden and intolerance of depression assessment and management on the patient (71.2%); and the complexity in differentiating the symptoms of terminal illness from the somatic symptoms of depression (53.0%)

rapidly effective depression interventions in low-burden manners [34]. This may be facilitated by better linkage and integration of the psychiatry services into the palliative care services [17, 35].

Similar to the United States palliative physician cohort, near 70% of current survey's respondents expressed desires for better collaboration with the psychiatry services [36]. At the clinical and health service levels, some strategies to improve palliative care and psychiatry collaboration might include: integrative multidisciplinary team [15, 36–38]; joint development of a tiered-referral model tailored to local health service needs [39]; and integrated clinician training via workshops and experiential training [35, 37, 38]. For research, palliative care and psychiatry researchers must collaborate to address barriers to the currently limited evidence base. On top of the barriers to depression care processes identified in this survey, other challenges include the effects of depression and terminal illnesses on participants' ability to consent and engage with research activities, and the ethical concerns of trial participants receiving potentially ineffective therapies [40, 41]. There is a need for integrated palliative care and psychiatry research that explores appropriate depression screening and assessment strategies and potentially rapidly effective interventions using feasible and inclusive trial designs in the very poor prognosis setting (e.g. n-of-1, Bayesian response-adaptive-randomisation, or well-designed prospective case-controlled studies) [26, 35, 42]. Developing consensus approaches between palliative care and psychiatry via Delphi and updating the existing guideline based on the currently limited evidence to guide depression care specifically for people with very poor prognoses need to be considered [16, 17]. Overall, better collaboration between palliative care and psychiatry is urgently required, optimising timely access to needed interventions, complementing the shortfalls of both disciplines, and ultimately improving care to affected patients [35, 37, 43].

Limitations

This study had low response rates, especially from the psychiatry cohort. These low rates were likely contributed by the COVID-19 pandemic, leading to clinicians focusing on COVID-19 related activities rather than non-COVID-19 research. It was possible that psychiatrists lacked interest or perceived a lack of relevance towards this topic due to their infrequent engagement with palliative care [35]. The low sample size limited the power for detailed subgroup analyses. The current survey did not include non-physician palliative clinicians (e.g. nurses and pastoral care) or psychologists. Furthermore, as the respondents were recruited only from the Australasia setting, the survey findings may not be generalised to non-Australasian contexts. Intrinsic to the study methodology, there was a risk of reporting bias where the reported practices deviate from the true practices. For depression interventions, various non-pharmacological interventions (e.g. supportive psychotherapy versus cognitive therapy) were not individually explored. Due to a technical fault, the survey question exploring psychostimulant use was initially unavailable to the first 28 ANZSPM respondents. Despite these limitations, the data collected still helped inform current practices and perceptions of some palliative physicians in Australasia. Lastly, while the prevalence data in Table 4 offered valuable insight into the prevailing perceived key barriers or challenges of depression care in the very poor prognosis setting among respondents, the prevalence data did not necessarily reflect the level of importance or influence of certain subcategories over another in optimising depression care. In fact, the domain subcategories reported less often such as the heterogeneity of depression concept and unsupportive societal attitudes might reflect that many clinicians were not cognisant of these topics, thus suggesting the need for improving awareness of these issues.

Conclusions

Palliative physicians perceived depression care in people with very poor prognoses to be complex and challenging. The lack of screening, heterogeneity in the depression assessment, and the generally reduced likelihood of intervening for depression in the very poor prognosis setting compared to that of better prognosis highlighted the need for better collaboration between palliative medicine and psychiatry in health service delivery, clinician training, and research.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12904-022-00901-y.

Additional file 1. Current palliative care physicians' and psychiatrists' practices, challenges and potential improvement strategies in assessing and managing depression in palliative patients with very poor prognoses.

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Authors' contributions

Under the supervision of DC, MA, and BD, WL designed the survey and collected the data. WL analysed the data with statistical support of SC and qualitative analysis support of MD. WL drafted the manuscript and DC, MA, BD, MD and SC provided critical revisions throughout. The author(s) read and approved the final manuscript.

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Availability of data and materials
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This project has been approved by the Human Research Ethics Committee of the University Technology Sydney (approval number: ETH19-4071). Implied written informed consents have been obtained from all participants by participants proceeding with the online anonymous survey after accessing the participant information cover sheet. All procedures were performed in accordance with the principles set by the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The author(s) declare(s) that they have no competing interests.

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Publisher's Note

Appendix 7. Focus Group of Palliative Physician an Consultation-Liaison Psychiatry (Journal of Palliative Care)

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A Focus Group Study of Palliative Physician and Consultation-Liaison Psychiatrist Perceptions of Dealing with Depression in the Dying

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Abstract

Objective: To ascertain palliative physicians' and consultation-liaison psychiatrists' perceptions of depression care processes in patients with very poor prognoses, exploring key challenges and postulating solutions. **Methods:** A qualitative focus group study involving three 1-h online focus groups (2 palliative medicine and 1 psychiatry) were conducted between November-December 2020. Fellows and trainees were recruited from Australian and New Zealand Society of Palliative Medicine (n = 11) and Royal Australian and New Zealand College of Psychiatrists (n = 4). Data underwent conventional qualitative content analysis. **Results:** Participants perceived depression care to be complex and challenging. Perceived barriers included: inadequate palliative care psychiatry skills with variation in clinical approaches; lack of supportive health infrastructure (poor access to required interventions and suboptimal linkage between palliative care and psychiatry); lack of research support; and societal stigma. Suggested solutions included integrating care processes between palliative care and psychiatry to improve clinician training, establish supportive health systems and promote innovative research designs. **Conclusions:** Developing clinician training, supportive health systems and innovative research strategies centering on integrating palliative care and psychiatry care processes may be integral to optimising depression care when providing care to people with very poor prognoses.

Keywords

depression, palliative care, psychiatry, terminal care, prognosis, focus groups

Introduction

Clinically significant depressive symptoms are prevalent in people with advanced life-limiting illnesses.[1,2] These can exacerbate physical and psycho-existential sufferings, worsen the quality-of-life for families and individuals, and deprive people from having meaningful social interactions for good closures at the end-of-life.[2–8] In the general palliative care population, assessment and management of such can be challenging due to co-existing symptom burdens, associated complications from physical illnesses, and often complex psychosocial dynamics.[2,9–11] Within this cohort, there is a subgroup with very poor prognoses measured in days-to-weeks. This subgroup may pose extra clinical challenges as they usually have poorer functional status and higher symptom burden than others while the usual interventions for depressive symptoms may not benefit in-time nor be tolerated.[1,12–16] For the purpose of this study, the term "depression" will be used to indicate clinically significant depressive symptoms that include various depressive disorders and depressive symptoms that fulfil thresholds of depression-specific assessment tools.[1,17–19]

There were studies that explored clinicians' perspectives towards delivering depression care in the general palliative care population, showing varying degrees of clinician confidence.[20–23] For people whose prognoses are in the range of days-to-weeks, these studies suggested that clinicians may have a sense of nihilism, and were less likely to assess or treat depression.[20–22] While palliative physicians and psychiatrists are integral parts of providing specialist depression care

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in the palliative care context,[24] no study explored their perceptions and approaches to depression care in people with very poor prognoses.

The authors undertook a survey of Australasian (Australia and New Zealand) palliative care physicians and psychiatrists to address such.[11] The survey identified low rates (40%) of depression screening with all participants having experienced diagnostic uncertainty, reporting assessment and management variations.[11] Less than 25% of participants reported more likely to intervene for major depressive disorder with non-pharmacological and/or typical antidepresants when life-expentancy is short.[11] A sense of "*therapeutic nihilism*" was described: "*Why assess it if there is little I can do about it?*"; "*Pointless if interventions (including psychosocial) will not be practical/acceptable.*" (Supplemental Material 1)[11] A qualitative study was subsequently needed to explore these issues in greater depth.

This study aimed to ascertain the perceptions of Australasian palliative physicians and psychiatrists regarding depression screening, assessment and management in the very poor prognosis setting (defined by an estimated life-expentancy of days-to-weeks), exploring key barriers to care and potential solutions.

Methods

Study Design & Methodology

This study is the second part of a mixed-methods study with a sequential explanatory design, informed by the methodology of pragmatism.[25–27] After conducting an initial predominantly quantitative survey that identified clinicians' practices and perceived barriers, this qualitative study used a focus group method for triangulation to gain insight into the survey findings and generate potential improvement strategies.[11,25,28]

Population & Recruitment

Eligible participants were palliative physicians and psychiatrists based in Australasia who were members of Australian and New Zealand Society of Palliative Medicine (consisting of general practitioners and specialist physicians with advanced training in palliative medicine) and Royal Australian and New Zealand College of Psychiatrists. Participants were recruited through emailed invitations distributed by both organisations. Initially only those who have completed the preceding survey (n = 9; 60.0%) were eligible.[11] Due to poor recruitment, the invitation was then expanded to include clinicians who were unsure of (n = 4; 26.7%) or denied survey completion (n = 2; 13.3%) by two subsequent email invitations using purposive and snowball sampling. Further email invitations were restricted by the organisations' dissemination policies.

Data Collection

Three focus groups (palliative care physicians: n = 2; CL psychiatrists: n = 1) each containing four to eight participants were conducted in November and December 2020, arranged according to participants' medical specialities. The focus groups were of one-hour duration, conducted online using Zoom. Only participants and the facilitators were present in the discussions. Each participant attended the focus group once.

Two facilitators (authors) conducted the focus group discussions. The primary facilitator was a male palliative care specialist and research fellow undertaking clinical care and doctoral studies on this topic. The secondary facilitator was a doctorally-qualified female academic with a background in psychology and experience in qualitative research in people with chronic and life-limiting illnesses. The primary facilitator was known to some palliative care participants as a clinical colleague, but not in a hierarchical relationship. The secondary facilitator was not known to any participants. While the primary facilitator facilitated the group discussion, the secondary facilitator moderated the discussion and recorded relevant field notes to aid data analysis.

Participants were emailed the initial survey results (inclusive of psychiatry results [n = 32] – Supplemental Material 1) and were informed that they would be asked to comment on these when attending the focus groups.[11] To begin each session, participants were asked about their general impression of depression in people with very poor prognoses. The survey results were then presented by the primary facilitator.[11] Following this, participants were prompted to comment on the survey findings, elaborate on the perceived reasons for clinical practices and challenges, and postulate potential improvement strategies using open-ended questions designed *a priori* (Supplemental Material 2).

Data Analysis and Reporting

The focus group discussions were video-recorded with participants' permissions. The audio recordings were transcribed using a professional transcription service. Primary facilitator checked transcripts for accuracy. The primary and secondary facilitators undertook conventional qualitative content analysis.[29,30] They independently read and re-read transcripts, coded text inductively, and created coding trees using NVivo 12. They met to rectify differences and consolidate codes into agreed categories through multiple discussions among them and the rest of the authorship team (consisting of researchers and clinicians with backgrounds of palliative medicine or psychiatry) until 100% consensus was reached. Aligning with the aim of this study, data are reported according to general perceptions, challenges, and solutions. Following inductive analysis, categories of challenges and solutions, broadly influenced by McLeroy's ecological framework, were applied post-hoc to organise data for reporting, as they reflect various levels of influence required to drive changes.[31] This article was written using the Consolidated Criteria for Reporting Qualitative Research (COREQ) framework.[32]

Results

Overall, fifteen clinicians participated (Table 1) - 11 palliative physicians and four consultation-liasion (CL) psychiatrists,

predominantly (> 90%) based in Australia with mean years of specialty experience of 10.7 (SD: 6.4) and 15.5 (SD: 5.1) respectively.

General Perceptions

When asked about their overall perceptions, the participants from each focus group described the topic of depression care in people with very poor prognoses to be "*complex*". A sense of disempowerment was expressed among the palliative physicians: "*uncertainty*", "*…it just makes me a bit depressed*", and "*[I feel] helpless*".

> "I think…there was the lack of skills [in depression screening, assessment and management] and we don't really know… We can't do anything, so then we're less likely to want to assess it." (Pallliative Physician 2)

In contrast, while still reflecting a sense of complexity towards the topic, CL psychiatrists conveyed a sense of empowerment and optimism that depression in this context is still "*worth treating*" and "*not necessarily inevitable*".

> *"I think people are more treatable than a lot of people think. People think there's an inevitability of depression and an understandability about it, but that's not always the case." (Psychiatrist 3)*

Comparisons of perspectives of palliative physicians and psychiatrists revealed differences in the perceived roles and needs of the two specialities, with palliative physicians describing the need for guided first-line depression care delivery while psychiatrists reporting inadequate resources to deliver second-line care (Table 2). Perceived key challenges and postulated potential solutions were described, synthesised *post hoc* into levels of influences informed by McLeroy's ecological framework (Table 3).[31]

Barriers & Challenges

Provider-level. Overall, participants described that clinicians lacked the required training and intra- and inter-disciplinary uniformity in approaches to depression care in people with very poor prognoses. Palliative physicians were perceived to lack the necessary psychiatric skills with poor knowledge of therapeutic options while psychiatrists were perceived to lack the required palliative medicine training to deliver optimal depression care at the end-of-life.

> "I think it's skills [identifying and responding to depression] that palliative care physician should have, but the simple fact is they don't, some of them." (Psychiatrist 3)

> "[psychiatrists] who aren't experienced in the area [palliative medicine], as soon as a patient expresses "I wish it was just all over," which is a pretty normal thing to say, they suddenly think they're suicidal…" (Palliative Physician 6)

Clinicians reported concerns of causing harm to patients and relationships through depression care processes: depression screening using lengthy questionnaires might "*fracture*" the therapeutic relationship; interventions may cause adverse effects while not producing timely benefits; and peer pressure against administering potentially helpful interventions that have little supportive evidence. In separate focus groups, two participants voiced depression can be perceived as a "*driver*" for people to make meaningful social interactions, and treating it might cause harm.

> "I wouldn't want to be robbing people of appropriate drivers to help people at the end-of-life (by treating their depression). The stress (depression) can be a driver to bring people together in a way if you do it right." (Palliative Physician 7)

> "Are we robbing people of appropriate sorrow by diagnosing them with depression and treating them?" (Palliative Physician 2)

Health system-level. Clinicians perceived a general lack of access to required liaison psychiatry and psychology services, especially those with palliative care expertise, even in urban settings where resources and skilled personnels tend to be more readily available.

> "It goes back to resources. It just keeps going back to it. You [palliative physicians] can screen all you want, but if there's nobody [liaison psychiatry and psychology services with palliative care expertise] there to help you as a palliative care physician, you might do a good job of it, but you might feel under-supported…" (Psychiatrist 4)

Access to potentially effective interventions was impacted by regulatory issues, contributed by the limited evidence-base in the literature.

> "The other issue that comes up with novel treatments [in context of ketamine] or non-standard treatments are the limitations of the evidence-base and regulatory issues, which vary from state to state." (Palliative Physician 1)

Participants noted that linkage and collaboration between existing palliative care and psychiatry services were often suboptimal. Negative clinician perceptions towards the other discipline were described to have contributed to the infrequent contact and late referrals. For example, some palliative physicians perceived undesirable assessment outcomes from psychiatry referrals.

> "My CL [Consultation Liaison] service at one site, definitely, everybody seemed to have 'adjustment disorder'…But I think sometimes it gets a bit tiring to see 'adjustment disorder'…it just affects how often I want to ask them to come and give help really…" (Palliative Physician 8)

Research-level. A lack of research with evidence to support various assessment methods and interventions in people with

Table 1. Participant Characteristics.

	Palliative Medicine (n = 11)		Psychiatry (n = 4)	
	Details	n (%)	Details	n (%)
Background / Subspecialties	General Practitioner	3 (27.3%)	Consultation Liaison	4 (100%)
	Specialist Physician	8 (72.7%)		
Position	Specialist	10 (90.9%)	Specialist	4 (100%)
	Trainee	1 (9.1%)	Trainee	0 (0%)
Had experiences with palliative care patients	Yes	11 (100%)	Yes	4 (100%)
Country	Australia	10 (90.9%)	Australia	4 (100%)
	New Zealand	1 (9.1%)	New Zealand	0 (0%)
Regionality of Work*	Urban	10 (90.9%)	Urban	4 (100%)
	Regional/Rural	1 (9.1%)	Regional/Rural	1 (90.9%)
Setting of Services*	Community (Home/Residential aged care)	9 (81.8%)	Community (Home/Residential aged care)	0 (0%)
	Outpatient Clinic	5 (45.5%)	Outpatient Clinic	2 (50.0%)
	Inpatient Palliative Care Unit /Hospice	6 (54.5%)	Inpatient Mental Health Unit	1 (25.0%)
	Consult	6 (54.5%)	Consult	3 (75.0%)
Public /Private*	Public	11 (100%)	Public	3 (75.0%)
	Private	3 (27.3%)	Private	3 (75.0%)
Previous Survey Completion	Yes	5 (45.5%)	Yes	4 (100%)
	Unsure	4 (36.4%)	Unsure	0 (0%)
	No	2 (18.2%)	No	0 (100%)

*Multiple response item (compared to other single response items).

very poor prognoses was a key challenge, as there was reluctance to enrol these individuals into clinical trials. While palliative physicians reported concerns around feasibility and burden of clinical trials on participants, CL psychiatrists voiced ethical concerns of patients possibly receiving ineffective interventions during randomisation.

> "…there is a lot of barriers with researching in this patient group because we don't have a lot of time to get to them, and also the burdens often catch up and you have to weigh up…often research has a lot of questionnaires…that can be very challenging in such a difficult time" (Palliative Physician 11)

> "I did a small pilot trial looking at ICBT [Internet-based Cognitive Behavioural Therapy] in people with advanced cancer, but you can't randomize them, you know…very ethically problematic thing to do. Like you can, but it would be really hard to go through the ethics board. And also personally I would find that hard!" (Psychiatrist 4)

Society-level. Stigma of mental health issues was reported as a barrier to care. Initiating patient discussion around psychological needs and having liaison psychiatry or psychology input was not observed by patients to be the norm, contributing to patients' resistance in depression care.

> "…a lot of patients, particularly in certain age groups where you never talked about psychiatric issues, and then when they're at the end of life and you start to bring that up, they get quite 'What do you mean?'" (Palliative Physician 2)

Potential Solutions

Overall, the potential solutions postulated by participants involved an integrative approach established upon the foundation of a better collaboration between both palliative care and psychiatry disciplines (Figure 1 & Table 3).

Provider-level

Screening. For better depression recognition, participants postulated that low-burden depression screening as part of a general screening for psycho-existential distress be added to the current generic symptom screening tool (eg, Palliative Care Outcome Collaboration Symptom Assessment Scale [PCOC SAS]) used in palliative care services.

> "..[Depression screening] being part of the PCOC [Palliative Care Outcomes Collaboration] scoring might be helpful, part of the standard scoring that we do before we see the patient…That might just help alert us there's something else that we need to screen for." (Palliative Physician 11)

Development of Consensus Approach. Participants perceived the need for palliative care and psychiatry to develop a consensus approach to care using best available evidence. The approach needs to be tailored to the skill-level of individual clinicians - a structured approach to guide less experienced clinicians, and a flexible approach relying more on clinical judgment for the more experienced.

Table 2. Comparison of Palliative Medicine and Psychiatry Cohorts.

Domains	Palliative medicine (differences)	Overlap/similarities	Psychiatry* (differences)
General "one-word" impression for this topic	• Sense of Disempowerment	• Complexity of topic	• Sense of Empowerment
Perceived role	• Breadth-Focus (Coverage of all competing distresses (physical and psycho-existential) • Implementing initial screening, assessment and management for depression	• Perceived differences in roles for each discipline	• Depth-Focus (Covering specific psycho-existential distresses) • Detailed/focused assessment and management of specific challenging mental health issues referred by palliative care
Screening & Assessment	• Require a more structured/ guided approach (eg, a framework or action plan)	• Methods need to be tailored to individual clinicians' skills	• Require flexibility/room for clinical judgement
Management	• Require more knowledge of non-pharmacological and pharmacological interventions	• Having issues with irrational prescribing of anti-depressants • Need to optimise non-pharmacological interventions	• Require more funding and resources to administer potentially effective interventions
Research	• Optimistic – perceiving potential solutions to improve research by modifying clinical trials designs	• Concerns of the potential harms outweigh the benefits for enrolling depressed patients with very poor prognoses patients into clinical trials	• Pessimistic - ethical concerns of clinical trials in this population
Service Integration/ Referral	• Palliative physicians' perception of undesirable outcomes from psychiatry assessment	• Agree with the need for *routine* contact/ liaison between palliative medicine and psychiatry	• Psychiatry's perception of the lack of skills of palliative physicians in depression care processes

*The psychiatrists' viewpoints here were represented by a small group of clinical liaison psychiatrists (n = 4), with no representation from general psychiatrists.

> "I felt like maybe we, as two groups, need to get together and talk about what is actually the best way to manage these patients' depression - because I think there are two very different disciplines, and two very different skill sets that we need to marry to come up with a best way to approach this treatment." (Palliative Physician 11)

Improve Clinician Training. Participants described that palliative physicians can be trained with low-burden approaches to depression care. Specifically,the training content may include: the use of ultra-short screening methods such as one- or two-item depression screening tools; the skills to differentiate and formulate the complex interplay of biopsychosocial aetiology during depression assessment[33]; and the ability to respond appropriately to depressed patients with the knowledge of potentially rapid-onset therapeutic options (ie methylphenidate and ketamine). Meanwhile, psychiatrists need the foundational knowledge of general management of symptoms and end-of-life issues. Clinician training can occur through establishing: regular interdisciplinary contacts; shared education; integrative advanced training; and formal education.

> "…increasing exposure to junior medical staff [including palliative care trainees] to psychiatry rotations, so that there's capacity building and so that people have a basic building block of how to actually do psychiatrist assessments and start treatment…That [integrative training between palliative care and psychiatry] would be excellent." (Psychiatrist 3)

Health system & service-level

Optimising Resources. While participants reported a need for more funding to better resource the palliative care and liaison psychiatry services, participants also postulated strategies to optimise interim resources. Community resources such as volunteers and community initiatives may be utilised to deliver necessary non-pharmacological interventions that do not necessitate psychiatry or psychology services. Strategies to improve current linkage between existing psychiatry and palliative care services may optimise resource access. This can include establishing routine palliative care–CL psychiatry multi-disciplinary team (MDT) meetings, ward rounds, and informal gatherings.

> "…that weekly [palliative care psychiatry multidisciplinary] meeting, like tomorrow I [psychiatrist] will discuss two new patients at that meeting with the broader team, and they [palliative care clinicians] just find that invaluable…it really up-skills them over time." (Psychiatrist 4)

Optimising Referrals. Participants postulated a tiered approach for psychiatry referral, involving palliative physicians performing first-line depression care using low-burden structured methods or guidance from psychiatry, followed by psychiatry input if further assessment and management are needed. Participants voiced that the referral criteria for each discipline need to be tailored to clinicians'

Table 3. Perceived Key Barriers and Challenges to Depression Care for People with Very Poor Prognoses and Postulated Solutions by Australasian Palliative Physicians and Psychiatrists.

Barriers/challenges	Postulated solutions
Provider Level	
• Palliative physicians and psychiatrists lacked training and uniformity in depression screening, assessment and management when caring for people with very poor prognoses, and reported concerns of causing harm to patients and relationships through the care processes.	• Introduce psycho-existential distress screening to existing generic symptom screening tools utilised in palliative care services (eg, Palliative Care Outcome Collaboration [PCOC]) to improve depression screening. • Develop consensus approach to care between palliative medicine and psychiatry that is tailored to individual clinician's skill-level. • Train clinicians with low-burden depression screening, assessment and management approaches via regular palliative care and psychiatry contacts (eg, shared education), including the ability to differentiate, formulate and respond appropriately to depression when caring for people with very poor prognoses.
Health Systems Level	
• The lack of access to required interventions and resources (eg, clinical psychology) and suboptimal palliative care and psychiatry service linkage with associated negative clinician perceptions towards the other specialty adversely impact on patient care.	• While advocating for funding to better resource palliative care and psychiatry services, interim resources can be optimised by utilising community resources (eg, volunteers and community initiatives) and strategies that improve existing palliative care and psychiatry service linkage (eg, integrative multidisciplinary team meeting and ward round). • Develop a tiered referral model for psychiatry services tailored to individual palliative care services. • "Deformalise" the psychiatry referral thresholds so that palliative physicias do not perceive the referrals to require prior establishment of provisional psychiatric disorders but clinically significant symptoms.
Research Level	
• Supportive evidence for screening, assessment and management of depression for people with very poor prognoses is lacking with clinicians concerned about the feasibility, burden and ethics of involving these people in experimental trials.	• Foster integrative research between palliative care and psychiatry, exploring various depression assessment and intervention methods and using innovative clinical trial designs to address feasibility and ethical concerns (eg, Pre-consent/N-of-1).
Society/Culture Level	
• Stigma of mental health issues could have affected depression assessment and management at the end-of-life.	• Rebrand psychiatric services as part of routine palliative care service provision to enhance patient acceptance of psychiatric assessment and interventions.

skills in individual local health services, including "deformalising" the referral processes to encourage earlier referrals.

> "…to de-formalise [psychiatry referral criteria] and allow [palliative] clinicians to simply flag potential 'mood problems'. We found similar with delirium, many of our multi-D[isciplinary] team were reluctant to use the word 'delirium' verbally or in the case notes as they felt they hadn't 'diagnosed' it properly. However when we encouraged them to just flag 'confusion' or 'altered behaviour', [clinical service provision improved]… Perhaps a similar approach could work for depression." (Palliative Physician 4)

Research-level. Despite participants voicing mixed feelings towards research in those with very poor prognoses, participants all agreed that collaborative research between palliative medicine and psychiatry in studying various assessment and management options is pivotal.

> "I think research are very important in our patient group and with the research then we'll be better guided on how we can manage these patients." (Palliative Physician 11)

To address the feasibility and ethical concerns of enrolling patients with very poor prognoses into experimental trials, modification of clinical trial designs was suggested (e.g., utilising pre-consenting method of consent or n-of-1 design).

> "I'm interested in n-of-1 trials. I've seen them used for other medications. I think that could be something that could be applied to palliative care" (Palliative Physician 7)

Society-level. At the societal level, clinicians thought "rebranding" psychiatric interventions and services by making them part of the routine palliative care service provision might reduce stigma of mental illness and enhance patient acceptance of psychiatric assessments and interventions.

> "…'rebrand' psychiatry in oncology and palliative medicine, so that like in chronic pain, psychology is just part of your assessment, because it's normal to need a psychologist or psychiatrist as part of your team to help manage and get your optimal outcome in a very difficult situation" (Palliative Physician 2)

Discussion

This study provides insights into the previous survey findings of perceived complexities of palliative physicians and psychiatrists when providing depression care for those with very poor prognoses.[11] It expounded upon the sense of nihilism reported in the survey, detailed the contributing challenges, and postulated solutions (Table 3).[11]

While patients might be fearful in eliciting their depression with treating clinicians, this study findings support that palliative physicians may also feel inadequately trained to initiate and effectively perform depression screening and assessment, perceiving these processes as time-consuming and burdensome for patients and themselves.[2,8,11,34–36] The concern of "*robbing people of appropriate drivers*" for good closure with important persons at the end-of-life by treating depression highlights the challenges for palliative physicians in differentiating pathological depressive syndromes (for which interventions may improve social engagement) from appropriate reactive sadness, where offering interventions beyond psychosocial support may cause harm.[2,16] The reported observation that inexperienced clinicians may consider more typical antidepressants instead of non-pharmacological interventions (eg, dignity therapy) as foundation and adding rapid-onset pharmacological agents with psychiatry inputs (eg, methylphenidate or ketamine) if indicated also highlight the need for better education and supportive infrastructure (eg, regulations towards methylphenidate prescribing).[2,35,37–39]

Meanwhile, the participating CL psychiatry cohort were skilled and experienced in treating patients with depression in this setting. Consistent with the literature, they perceived depression in advanced life-limiting illnesses to be potentially treatable, even in those nearing death.[2,10,16,39] However, they acknowledged that they were a minority and felt under-resourced. This is echoed by the perception that psychiatrists who are skilled and experienced in palliative care are lacking, with some avoiding this field.[2,23,35] In fact, one previous psychiatry survey respondent reported "*Very few psychiatrist are comfortable working in the clinical space*" (Supplemental Material 1). To improve care, there needs to be an increased awareness of the importance of palliative care psychiatry with funding prioritised.[2,24]

The postulated solutions by participants, as discussed below, centered around care process integration between palliative care and psychiatry, consistent with strategies suggested for improving palliative care and psychiatry collaboration in the general palliative care population.[24,40,41] While these strategies were postulated to facilitate consensus in approaches and amalgamate the forte of both specialties, their effectiveness to improve patient outcomes for people with very poor prognoses and the associated implementation barriers warrant future studies.

Strategies and Implications

Provider level. The suggested routine depression screening added to an established generic symptom screen in palliative care services such as the PCOC SAS may be helpful, though the optimal depression screening method in this very poor prognosis subpopulation is contentious and requires further studies.[40,42,43] Palliative physicians and psychiatrists should learn both psychiatric and palliative care skills relevant to this field.[11,23] While evidence informing effectiveness of specific training strategies is scant in this setting, the postulated strategies reinforced by the literature include: informal education through integrative MDT meetings, clinics and ward rounds; and building formal integrative training opportunities such as joint educational seminars, clinical placement of trainees in the other specialty, and mandatory teaching in college training curricula.[22,24,40,44–46] As postulated, training content may include skills for both disciplines to work collaboratively to deliver depression screening, assessment and management in low-burden manners, facilitating potentially effective psychotherapies as foundation (eg, dignity and meaning-centered therapies), complemented by rapid-onset pharmacological agents (eg, methylphenidate, and esketamine) as required.[16,22–24,35,37–41,47–50]

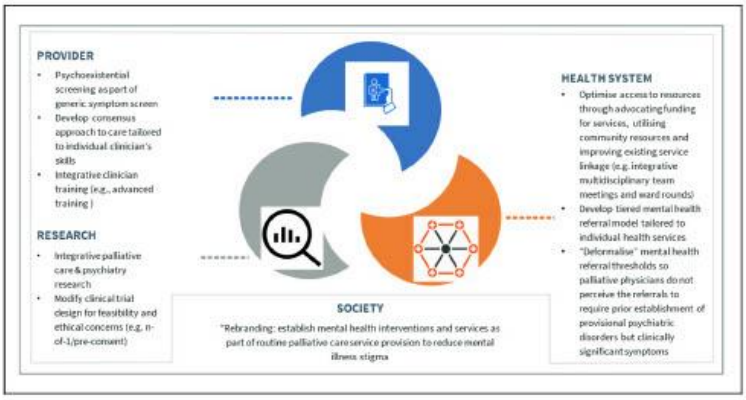

Figure 1. Care Process Integration of Palliative Medicine and Psychiatry – Postulated Solutions by Participants.

Health system & policy level. Pervious survey identified that palliative physicians perceived a lack of access to required psychiatric resources despite Australasia having some of the most well-resourced health system per capita internationally.[11,51] As found in the focus group discussions, a key contributor may be the lack of supportive infrastructure with inadequate liaisons between existing palliative and psychiatric services.[2,46] Health services need to prioritise efforts and fundings that promotes palliative care and psychiatry service integration and timely depression interventions (eg, funding for psychiatry presence and exemptions to regulatory restrictions for psychostimulants).[2,24] As suggested by participants, community volunteers can be trained to provide general emotional support or counselling to relieve the system burden.[52,53] Furthermore, nurses and social workers from both disciplines may be trained to perform first-line depression assessment and interventions for palliative care patients.[40,54–56] In line with the postulated solutions, most depression cases may be adequately managed by the treating palliative care team provided there is appropriate training, and a referral to psychiatry can be initiated when escalation of care is required.[16] The pespectives of various MDT members (eg, nurses, pastoral care workers, and psychologists) and ways to leverage their strengths to deliver care warrants future exploration.

Research level. While there is a paucity of palliative care psychiatry implementation studies to guide changes in this field, as perceived by participants, there lacks high-quality evidence of effective interventions when prognoses are poor.[11,13,15] Integrative palliative care and psychiatry research is needed. Randomisation, arguably, can be ethical if there is clinical equipoise (eg, dignity therapy and methylphenidate trials).[15,37,39,57,58] Researchers need to consider innovative strategies to minimise burden and maximise potential benefits for participants. Feasibility studies prior to phase III trials and the use of alternative inclusive and supportive designs (eg, pre-consent, n-of-1, and Bayesian response adaptive randomisation) warrant considerations.[59,60] Using high-quality prospective case-control studies or modifying Naranjo criteria in phase IV pharmacovigilance study settings to imply causal relationship for interventions may also be possible.[61]

Limitations

The study's key limitation is the small number of focus groups conducted. As suggested by participants, the poor recruitment might resulted from clinicians prioritising COVID-19 related clinical activities over non-COVID-19 research, potential avoidance by general (non-CL) psychiatrists from perceived lack of relevance or interests, and the limited capacity of participating organisations in disseminating study invitations.[24,35] Subsequently, recruitment expanded to include non-survey respondents. Meanwhile, maximum variation and data saturation may not have been reached, especially in the psychiatry cohort, and the comparison between palliative care and psychiatry cohorts is hypothesis-generating in nature.

Conclusion

Palliative physicians and psychiatrists perceived depression care in people with very poor prognoses to be complex and challenging, contributed by the lack of clinician training, interdisciplinary collaboration, research, and supportive societal attitudes. Developing clinician training, supportive health infrastructures and innovative research strategies centering on integrating palliative care and psychiatry care processes may be helpful.

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Author Contributions

Under the supervision of DC, MA, and BD, WL and MD designed the focus group study protocol and collected the data. WL and MD analysed the data. WL drafted the manuscript and DC, MA, BD, and MD provided critical revisions throughout.

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Research Ethics and Patient Consent

This project has been approved by the Human Research Ethics Committee of the University Technology Sydney (approval number: ETH19-4071). All participants provided written informed consent.

Data Management and Sharing

Anonymous focus group data can be requested from the corresponding author if required.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Appendix 8. Online Survey Questions

DEMOGRAPHICS

1. Which of the following best represents you?
    a. Specialist/Fellow
    b. Trainee
    c. Other (Please specify)
2. What is your primary specialty?
    a. Palliative Medicine
    b. Psychiatry
    c. Others (Please specify)
3. Apart from your primary specialty, do you have another training background?
    a. General Practice
    b. Physician Training
    c. Psychiatry
    d. Critical care (Emergency, Intensive Care, Anaesthetics)
    e. Others

4. Which part of Australasia do you primarily work in?
    a. Australia
    b. New Zealand
    c. Other (Please Specify)

5. Years since medical graduation
    a. < 5
    b. 5-9
    c. 10-14
    d. 15-19
    e. 20 or more

6. Your age (year old)
    a. 21-30
    b. 31-40
    c. 41-50
    d. 51-60
    e. 61-70
    f. 71-80
    g. > 81

7. Your gender:
    a. Male
    b. Female
    c. Other
    d. Rather not say

8. On the usual basis, how many hours per week do you take on the role as a clinician on average?
    a. <10
    b. 10-19

c. 20-29
d. 30-39
e. 40 or more

9. Where do you spend time in your clinical role (Tick all that apply)?
    a. Community setting (Patient's home, group home and / or residential aged care facilities)
    b. Outpatient Clinic
    c. Consultative service in acute hospitals
    d. Acute inpatient care (palliative care or psychiatry wards in acute hospital)
    e. Subacute hospital (e.g. palliative care unit / hospice, subacute psychiatry unit)

ENCOUNTER

10. Have you encountered depression in palliative care patients with very poor prognoses (defined in this project as those with estimated prognoses in the range of days to weeks, characterised by them being mostly bedbound)?
    a. Yes → (Continue survey)
    b. No → (Jump questions containing palliative care patients with very poor prognoses using branching logic electronically)
    c. Other (Please – Specify)

ASSESSMENT

11. Do you screen for depression in palliative care patients?
    a. Yes → continue
    b. No → jump to Q15
    c. Depends (Please – Specify)

12. How do you screen for depression in these patients? (Tick all that apply)
    a. By seeing / interviewing the patient
    b. By using a tool (Please select / name the tools – drop down menu: Hospital Anxiety and Depression Scale, asking one item question: "Are you depressed?", asking two items "Are you depressed", "Have you had little interest or pleasure in doing things" (e.g. Patient Health Questionnaire-2), Geriatric Depression Scale, Beck's Depression Inventory, Others [Please-Specify])
    c. By asking the family / carers
    d. By asking other health professionals involved in the care (e.g. nurses, social worker, clinical psychologist, pastoral care worker)
    e. Other (free-texts)

13. For the sub-group of palliative care patients with very poor prognoses, do you screen?
    a. Yes → continue
    b. No → jump to Q15

c. Depends (Please – Specify)

14. Is your method of screening for depression in palliative care patients with very poor prognoses different to your method of screening in other palliative care patients?
    a. No different
    b. Different (Please specify the differences using free text)
    c. Depends (Please – specify)

15. Do you exclude somatic symptoms of depression (e.g. changes in weight, sleep, fatigue and inability to concentrate) when assessing for depression?
    a. In palliative care patients without very poor prognoses (Drop down list: Exclude / Include / Depends (Please – Specify)
    b. In palliative care patients with very poor prognoses (Drop down list: Exclude / Include / Depends (Please – Specify)

16. What do you think are the key challenges/ barriers to effective **assessment** of depression in palliative care patients with very poor prognoses? (List up to 3 with free-text)
    a.
    b.
    c.

MANAGEMENT

17.

I. (Palliative Care Physician only) What would you usually do when you encounter palliative care patients with very poor prognoses with debilitating depression that affects their functional ability but you are uncertain of the cause (Tick all that apply)?
    a. Treat the depressed mood (using non-pharmacological and/or pharmacological interventions)
    b. Request for a second opinion from other palliative care colleagues
    c. Request for psychology input
    d. Request for psychiatry input
    e. Other (Please specify)
    f. That has not happened to me

II. (Psychiatry Physician only) What would you usually do when you encounter palliative care patients with very poor prognoses with debilitating depression that affects their functional ability but you are uncertain of the cause (Tick all that applies)?
    a. Treat the depressed mood (using non-pharmacological and/or pharmacological interventions)
    b. Request for a second opinion from other psychiatric colleagues
    c. Request for psychology input
    d. Other (Please specify)
    e. That has not happened to me

18. Do you usually ascertain whether the depression experienced by the patient is the first or recurrent episode?
    a. In palliative care patients without very poor prognoses (Drop down menu: Yes / No /Depends (Please specify)
    b. In palliative care patients with very poor prognoses (Drop down menu: Yes / No /Depends (Please specify)

19. Comparing the treatment of major depressive disorder in palliative care patients with very poor prognoses to treating that in the other palliative care patients, how likely are you going to use each of the following treatment during your routine practice?
    0 = I don't use this treatment for treating major depressive disorder
    1 = Much less likely than in the other palliative care patients
    2 = Less likely than in the other palliative care patients
    3 = No difference to the treatment in the other palliative care patients
    4 = More likely than in the other palliative patients
    5 = Much more likely than in the other palliative patients

a. Non-pharmacological interventions (e.g. supportive psychotherapy / counselling, cognitive therapy)	0, 1, 2, 3, 4, 5
b. Typical antidepressant	0, 1, 2, 3, 4, 5
c. Psychostimulant (e.g. methylphenidate, modafinil)	0, 1, 2, 3, 4, 5
d. Atypical antipsychotics (e.g. risperidone, olanzapine)	0, 1, 2, 3, 4, 5
e. Benzodiazepine	0, 1, 2, 3, 4, 5
f. Novel medication / experimental trials (e.g. ketamine, esketamine nasal spray)	0, 1, 2, 3, 4, 5
g. Electroconvulsive therapy	0, 1, 2, 3, 4, 5

20. What do you think are key challenges/ barriers to effective **management** of depression in palliative care patients with very poor prognoses? (List up to 3 using free-text)

a.
b.
c.

PSYCHIATRY LINKAGE

For palliative care physicians only:

21. For assessment and management of depression in the overall palliative care setting, on average how often have you asked psychiatry for input? (1= Never; 2 = yearly or longer; monthly or longer; 4 weekly or longer 5 daily or longer)
22. For patients with depression and palliative care needs, on average how often have you been asked by psychiatry to provide palliative care management advice? (1= Never; 2 = yearly or longer; monthly or longer; 4 weekly or longer 5 daily or longer)
23. For optimal patient care, do you think contact frequency with psychiatry should be: (more frequent; less frequent; about right; others)

For psychiatrists only:

21. For patients with depression and palliative care needs, on average how often have you ask palliative care for management input? (1= Never; 2 = yearly or longer; monthly or longer; 4 weekly or longer 5 daily or longer)
22. For assessment and management of depression in the overall palliative care setting, on average how often would you get asked by palliative care for input? (1= Never; 2 = yearly or longer; monthly or longer; 4 weekly or longer 5 daily or longer)
23. For optimal patient care, do you think contact frequency with palliative care should be: (more frequent; less frequent; about right; others)

Thank you very much for participating in this survey. This is the end of the survey.

If you are willing participate in the subsequent one-hour workshop / webinar (alongside other surveyed clinicians in the same discipline) to learn about survey results, discuss more about issues and challenges in this setting and offer potential strategies for improvement, please kindly leave your contact detail using a separate online link attached in this email. This will help us organise this workshop/ webinar.

(A separate online link in this email is used for registering your contact details to ensure that the anonymity of this survey is maintained – i.e. your *personal information will not be attached to your survey results).*

Appendix 9. Pre-Online Focus Group Materials

Depression Care in the Dying: Current Practices, Challenges and Ways Forward: Pre-Online Focus Group Materials

Background

- Clinically significant depressive symptoms affect 1 in 2 individuals with extremely short prognoses (in the range of days to weeks).
- Assessment and management of depression in this context can be particularly challenging
- Little is known about the approaches of Australasian palliative physicians and psychiatrists in this context.

Aim

- To explore the current approaches of Australasian palliative care physicians and psychiatrists to depression assessment and management in palliative patients with extremely short prognoses (in the range of days to weeks), identifying key barriers, and generating potential improvement strategies.

Methods

- Mixed methods study – explanatory sequential design:
  1. Initial anonymous online survey distributed by Australian and New Zealand Society of Palliative Medicine (ANZSPM) and Royal Australian and New Zealand College of Psychiatrists (RANZCP)
  2. Subsequent online focus group

Results

- ANZSPM: 79 out of 522 responses (15.1%)
- RANZCP: 31 out of 6655 (0.5%)
- Only results from palliative medicine (n = 72) and psychiatry (n = 32) are reported here to address the research aim (n = 104).
- 39.4% of clinicians screen for depression in patients with extremely short prognoses.
- The majority (71.9%) of clinicians use the same methods of screening in patients with extremely short prognoses and general palliative patients.
- More palliative physicians reported using screening tools than psychiatrists (47.4% vs 21.7%; p = 0.044).
- Most common screening tool (43.8%) = Ultra-short two item questionnaire
- Majority of clinicians include somatic symptoms when assessing depression in patients with better prognoses (50.5%), but exclude somatic symptoms for those with extremely short prognoses (38.0%).
- Most clinicians (≥ 85%) ascertain whether a depression episode is first or recurrent, regardless of the prognoses.
- All clinicians who encountered depressed patients with extremely short prognoses were uncertain of the cause of depression at times.
- Most clinicians (> 80%) would treat the depressed mood despite being uncertain of the cause.
- Non-pharmacological interventions (97.7%), followed by typical antidepressants (96.6%), were the most commonly used interventions for treating MDD in the extremely short prognoses setting.
- Out of those who use non-pharmacological interventions, significant more psychiatrists reported that they are “more likely” to use non-pharmacological interventions than palliative physicians (45.5% vs 18.2%; p < 0.01).
- The majority of clinicians, when comparing the likelihood of using various interventions to treat MDD in the extremely short prognoses setting (vs better prognoses setting):
  - Reported the same likelihood of using non-pharmacological interventions (42.0%)
  - Were less likely to use typical antidepressants (48.9%)
  - Did not use psychostimulant (44.6%), atypical antipsychotics (31.8%), benzodiazepines (33.0%), novel treatment or experimental trials (69.3%), and electroconvulsive therapy (61.4%).
- Compared to palliative physicians, more psychiatrists reported using:
  - Atypical antipsychotics (90.9% vs 60.6%; p = 0.02)
  - Benzodiazepines (95.5% vs 57.6%; p < 0.01)
  - Novel medication / experimental trials (45.5% vs 25.8%; p < 0.001)
  - Electroconvulsive therapy (86.4% vs 22.7%; p < 0.001)
- Majority of clinicians (Palliative: 72.7%; Psychiatry: 57.1%) are supportive of improved collaboration between palliative care and psychiatry through more frequent contact

Key Barriers for Depression Assessment and Management in the Extremely short prognoses Context

1. Clinical Complexity
2. Attitudes
3. Communication Challenges
4. Clinician Skills & Training
5. Services, Access & Resources

THEMES	QUOTES
1. Clinical Complexity	• "Complexity of interaction between physical/psychological/spiritual and social dimensions"
a. Challenging diagnostic differentiation	
ii. Normal vs Pathological	• "Hard to distinguish from normal grief"
iii. Depression vs terminal illness symptoms	• "Usually hard to tease out how much is depression and how much is part of dying process"
iv. Between depressed-mood syndromes or differentials (e.g. existential distress, demoralisation, adjustment disorder, organic brain syndrome / delirium)	• "Challenges differentiating demoralisation from major depression" • "Distinguishing between adjustment and depression" • "Misattribution - eg. depression with psychotic symptoms being attributed to delirium"
b. Therapeutic Efficacy - Lack of therapeutic options that are rapidly effective in the context of the extremely short prognoses	• "Lack of time for efficacious pharmacological AND non-pharmacological management to take effect "
c. Frailty, Burden & Intolerance	• "Fatigue, nausea, pain" and "cognitive impairment"…"too unwell to engage in psychology" or unable to "partake in e.g. CBT [cognitive behavioural therapy] meaningfully" • "Difficulties with the oral route" • "Lack of effective medication which will make a difference without causing unnecessary side effects"
d. Prioritisation - Prioritisation of physical or other psychosocial & spiritual co-existing issues, symptoms or life goals	• "Competing priorities - physical symptoms and planning for end-of-life are often more pressing"
2. Attitudes	
a. Nihilism / Futility	• "Why assess it if there's little I can do about it?" • "Pointless if interventions (including psychosocial) will not be practical/acceptable"
b. Acceptance / "Normalisation	• "Acceptance that this [depression] is a normal part of end of life"
c. Ambivalence	• "Deciding how actively/assertively to treat" • "Balancing respecting the patients` wishes to die vs excluding treatable causes" • "Weighing up benefits of treatment and of assertive treatment against loss of dignity"
d. Resistance / Disinclination of patients, public, family or clinicians/staffs	• "Loss / lack of interest" • "Stigma" • "Pressure from other health care professionals not to treat patients as they are dying" • "Fear for family" • "Family not willing to engage non-pharm [interventions]" • "Disinclination to involve psychiatry but psychology or religious leaders at this stage"
3. Communication Challenges (Inadequate information for assessment and management of depression)	• "Not understanding patients well enough" • "Reduced ability to communicate by the patient" • "Language / cultural barriers" • "Lack of clear and collateral history" and "past history of depression/ psychiatric treatment"

4. Clinician Skills & Training	• "Limited skills in psychiatric assessment (my last psychiatry placement was as a 3rd year medical student)" (palliative)
	• "Very few psychiatrist are comfortable working in the clinical space" (psychiatry)
	• Patient-Clinician Interaction:
	  ○ "Transference" - an unconscious transfer of feelings and attitudes from a person or situation in the past onto the current clinician that is partly inappropriate
	  ○ "Counter-transference" - the response produced in the clinician by transference

5. Services, Access & Resources	
a. Suboptimal palliative care and psychiatry service access and delivery	• "Inadequate funding for psychologists, social workers"; "lack of funding for travel time of staff to see at home"; "lack of staff resource" • "Lack of psychology/psychiatry support" • "Lack of time to sit down and chat with patients in depth about their mood regularly" • "Not enough time to devote for non-pharmacological approaches". • "Under/ late referrals" to both palliative care and psychiatry services
b. Lack of access to needed depression interventions (e.g. cognitive behavioural therapy, music therapy, or psychostimulants)	• "Lack of access to resources for non-pharmacological management e.g. psychology, music therapy" and "rapid-acting medications like modafinil" and "Ritalin [methylphenidate]"
c. Lack of physical space	• "Lack of private interview space in acute ward"
d. Lack of evidence & guidelines in the literature were also noted to inhibit optimal care	• "Lack of validated tools" • "Lack of defined criteria for diagnosis of depression in this group of patients"

	• "Uncertainty regarding the best treatment for this population/limited evidence base"

Appendix 10. Focus Group Guide

The below list of illustrative questions will be used as a guide for focus groups moderators to frame their questions. They will question around the palliative care clinicians' and psychiatrists' depression assessment and management practices, perceived challenges and potential improvement strategies. Open-ended question will be used along with prompts and probes to facilitate discussion.

1. Discussion of survey results of clinician practices
    - Clinician perspectives of Assessment /Management of Depression
        - "The survey result showed that X% of palliative care clinicians and Y% of psychiatrist (do [assessment / management behaviour])."
            - "Can you tell me what comes to mind when you hear this? What do these results mean to you?"
        - "How do you:":
            - 1. "assess / manage depression in those with extremely short prognoses?";
            - 2. "[help/support] patients' loved ones /family?""
        - "What other factors or conditions do you think should be considered while [assessing / managing depression in this context]?"
            - Probes:
            - "Any other associated medical conditions that would be considered? For example, delirium? Metastases to brain? Drug and alcohol?"
            - "Any other factors that you think is important to consider? For example, what the person's or their family's wish is? Or any unfinished business?"

- Perceptions of links between psychiatry and palliative care
    - “In delivering depression care for those with extremely short prognoses”:
        - “What is the role of pall care?”
        - “What is the role of psych?”
        - Can you tell me about a situation where they might overlap/collaborate?
        - (Prompt) When would you ask for psych / palliative care support?”

2. Discussion of survey results of perceived challenges (assessment /management of depression)
    - “What is your impression of [results of perceived challenges]?”
    - In what way is this true/not true in your experience?
    - (Prompt) “Can you tell me a bit more about that? can you give me an example?”

3. Potential Improvement Strategies
    - “How do you think we can improve depression care for those with extremely short prognoses?”
    - If need prompting, then, direct the discussion into various aspects of depression care:
        - Assessment /Management of depression
        - Linkage between palliative care and psychiatry

Appendix 11. SKIPMDD protocol manuscript (BMJ Open)

BMJ Open

Study protocol for SKIPMDD: subcutaneous ketamine infusion in palliative care patients with advanced life limiting illnesses for major depressive disorder (phase II pilot feasibility study)

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ABSTRACT

Introduction Major depressive disorder (MDD) in people with advanced life-limiting illnesses can have significant impact on the quality-of-life of those affected. The management of MDD in the palliative care setting can be challenging as typical antidepressants may not work in time nor be tolerated due to coexisting organ dysfunctions, symptom burden and frailty. Parenteral ketamine was found to exhibit effective and rapid-onset antidepressant effect even against treatment-resistant depression in the psychiatric population. However, there is currently neither feasibility study nor available prospective study available to inform of the safety, tolerability and efficacy of such for MDD in the palliative setting.

Methods and analysis This is an open-labelled, single arm, phase II pilot feasibility study involving adult patients with advanced life-limiting illnesses and MDD across four palliative care services in Australia. It has an individual dose-titration design (0.1–0.4 mg/kg) with weekly treatments of subcutaneous ketamine infusion over 2 hours. The primary outcome is feasibility. The secondary outcomes are related to the safety, tolerability and antidepressant efficacy of ketamine, participants' satisfaction in relation to the trial process and the reasons for not completing the study at various stages. The feasibility data will be reported using descriptive statistics. Meanwhile, side effects, tolerability and efficacy data will be analysed using change of assessment scores from baseline.

Ethics and dissemination Ethics approval was acquired (South Western Sydney Local Health District: HREC/18/LPOOL/466). The results of this study will be submitted for publication in peer-reviewed journals and presented at relevant conferences.

Trial registration number Australian New Zealand Clinical Trial Registry Number: ACTRN12618001586202; Pre-results.

Strengths and limitations of this study

- This study may provide key feasibility information for a future definitive study in the palliative care setting and inform the safety, tolerability and the antidepressant activity of ketamine for this population.
- Subcutaneous ultralow-dose infusion (<0.5 mg/kg) via an individually tailored dose titration design will likely maximise acceptability and tolerability for palliative patients, though there is less evidence for this approach compared with the conventional ketamine administration regimen (intravenous 0.5 mg/kg).
- The use of Endicott criteria for the diagnosis of major depressive disorder in the palliative care setting reduces the confounding effects of symptoms of terminal illnesses.
- The use of standard psychiatry research instruments allows direct comparison of this trial with other psychiatric trials, while maintaining the use of familiar oncological and palliative care trial instruments for safety monitoring.
- Inability to inform definitive effectiveness of ketamine (not blinded randomised controlled trial).

INTRODUCTION

Major depressive disorder (MDD) is common and can be severely distressing in individuals with advanced life-limiting illnesses. It affects approximately 10%–15% of individuals in the palliative care setting.[1–3] MDD can significantly impact the quality-of-life of those affected and may be associated with a sense of worthlessness and the desire for hastened death.[4–7]

The assessment and management of MDD can be challenging in the palliative care setting, particularly in the presence of substantial medical comorbidities when the prognosis is limited to only days to weeks.

The symptoms of advanced-life limiting illnesses can confound the assessment of MDD.[8] Patients may develop severe fatigue, delirium or pain, inhibiting comprehensive psychiatric assessment and engagement with psychotherapeutic interventions.[9 10] Pharmacologically, typical antidepressants may take up to 4 weeks to see the clinical benefit.[11–13] Even psychostimulants such as methylphenidate with faster onset of actions provide limited clinical utility due to the inability to administer these medications orally towards the end-of-life.[9 14–20]

Ketamine is a noncompetitive N-methyl-D-aspartate receptor antagonist known for its anaesthetic and analgesic use.[21–25] Recently, there is a growing evidence that subanaesthetic doses of ketamine can also provide antidepressant effects with rapid onset, even against treatment-resistant MDD.[26–35] The proposed mechanism of action has involved increasing synaptogenesis and neural plasticity secondary to the rapid rise in the brain extracellular glutamate level.[36] Additionally, it may induce alpha-amino-3-hydroxy-5-methyl-4isoxazeolepropionic acid receptor activation and brain-derived neurotrophic factor in the prefrontal cortex and hippocampus.[36] The onset of its antidepressant effect may be as rapid as 2 hours after administration and can potentially last for up to 1 week after a single bolus dose.[37] With repeated boluses, the effects may last up to 12 weeks.[27 30–34 36 37] According to the meta-analysis, the response rate of ketamine has been high with OR of 9.1 (95% CI 4.28 to 19.34) at 24-hours postintervention.[29] Meanwhile, it is generally well tolerated in the general psychiatric population, who are younger with fewer comorbidities compared with the palliative population.[26 28 33 34] Although there were reports of mild transient psychotomimetic and dissociative symptoms, and the potential for the acute elevation of blood pressure, which mostly resolves within 4 hours of administration, ketamine has not been associated with significantly serious immediate or short-term adverse effects.[26 27 33–35 38]

Despite the evidence for treatment of MDD in general psychiatry, the antidepressant effect of ketamine has not been well studied in the palliative care population. To date, there are only case reports and case series of intramuscular and intravenous ketamine, an open-label proof-of-concept trial using oral ketamine and a retrospective study by Iglewicz (2015), demonstrating its effect in the hospice setting.[27 39–43] There has been no randomised controlled trial (RCT) to inform the definitive effectiveness of ketamine as an antidepressant to treat MDD in the palliative care population. The reasons may be manifold. Participant recruitment towards the end-of-life may be challenging due to competing priorities of managing difficult physical symptoms and other life priorities. The effects of advanced life-limiting illnesses and anhedonia from depression might limit potential participants' ability to engage with or even consent to the trial.[44] Despite the psychiatric evidence, the pharmacological profile of ketamine for depression in the context of very poor functional status and organ dysfunction is not well understood. Not only are participants at risk of intolerance, the efficacy of ketamine at doses that might improve tolerability (ultralow doses of <0.5 mg/kg) in this population is also uncertain.[25] Furthermore, clinicians' general tendency to under-recognise, underassess and undertreat depression in advanced life-limiting illnesses can make conducting a definitive RCT of ketamine for depression in this setting challenging.[45–48]

Given these potential challenges of conducting a definitive RCT of ketamine as a rapid-onset antidepressant in this population, a feasibility study is required to inform the acceptability, safety, tolerability and activity of subanaesthetic doses of ketamine. These piloting data may serve as foundations for the larger RCT using an individually tailored dosing approach of ketamine.

AIM AND OBJECTIVES

The primary objective of this study is to determine the feasibility of ketamine subcutaneous (SC) infusion for MDD in palliative setting, measured by the numbers of consented patients who have been screened, treated and completed the study (ie, received weekly dosing of SC ketamine and assessment up to 8 weeks).

The secondary objectives are to determine the safety, tolerability, acceptability and efficacy of the treatment using an individually tailored dose titration approach.

METHODS AND ANALYSIS

Study design

The study is a pilot phase 2 multicentre feasibility study. It has an open-labelled, individual dose-titration design with all participants receiving ketamine SC infusion. The rationale for this design is discussed below.

Population and eligibility criteria

The target population involves patients with advanced life-limiting illnesses and MDD in the acute hospital, palliative care units and the community of the following Australian palliative care services: Liverpool Hospital, Braeside Hospital, Calvary/St George Hospitals and Sacred Heart/St Vincent Hospitals. The inclusion criteria are: (1) adults (≥ 18-year old), (2) known to palliative care services with palliative intent of treatment for irreversible life-limiting illnesses, (3) Patient Health Questionnaire-2 (PHQ-2) score ≥3 on screening, (4) MDD diagnosed by Endicott criteria (table 1) diagnosed by trained personnel,[8 49] (5) clinically significant depression severity defined by Montgomery-Asberg Depression Rating Scale (MADRS) Depression Severity Score ≥16, (6) willing and able to comply with all study requirements and (7) signed, written informed consent for the study.

The exclusion criteria will be:

- Australian-modified Karnofsky Performance scale (AKPS) score=10.
- Methylphenidate use in the last 4 weeks.
- Changes to antidepressant doses in the last 2 weeks before the commencement of ketamine.

Table 1 DSM-IV symptoms of major depressive disorder and Endicott substitute symptoms (Endicott criteria)

DSM-IV symptoms	Endicott substitute symptoms
Depressed mood most of the day*	
Marked diminished interest or pleasure in all, or almost all, activities most of the day (Anhedonia)*	
Weight loss or gain (>5% body weight in a month)/change in appetite	Depressed appearance
Insomnia or hypersomnia	Social withdrawal or decreased talkativeness
Psychomotor agitation or retardation	
Fatigue or loss of energy	Brooding, self-pity or pessimism
Feeling of worthlessness or excessive or inappropriate guilt	
Diminished ability to think or concentrate, indecisiveness	Lack of reactivity; cannot be cheered up
Recurrent thoughts of death, or suicidal ideation or planning, or a suicide attempt	

*One of these symptoms must be present for a diagnosis of major depressive disorder. Each symptom must also meet severity criteria of 'most of the day' or 'nearly every day" with a duration of greater than 2 weeks. The symptoms must cause clinically significant distress or impairment. They are not due to a physiological effect of a medication or general medical condition, and must not be accounted for bereavement.

- Ketamine use in the last 4 weeks.
- Previous significant adverse effect or hypersensitivity to ketamine.
- Concurrent phenobarbitone use.
- Factors of increased risk of intracranial pressure:
  i. Recent ischaemic or haemorrhagic cerebral vascular accident in the last 1 month.
  ii. Brain tumours with symptoms and signs of increased intracranial pressure.
  iii. Seizure in the last 6 months.
  iv. Head trauma with symptoms of increased intracranial pressure.
  v. Hydrocephalus.
  vi. Uncontrolled nausea, vomiting and headache (eg, from cerebral metastases, trauma), ≥ grade 3 nausea despite one line of antiemetics.
- Factors of increased risk of sympathomimetic response (hypertension and tachycardia) with associated complications
  i. Uncontrolled hypertension with systolic blood pressure ≥160.
  ii. Tachycardia with heart rate ≥120/min.
  iii. Symptomatic ischaemic heart disease (eg, exertional angina) and decompensated heart failure with New York Heart Association (NYHA) class III and IV symptoms.
  iv. Uncontrolled hyperthyroidism (low Thyroid Stimulating Hormone [TSH] with high T3 and/or T4).
  v. Diagnosis and history of porphyria.
- Factors of increased risk of intraocular pressure with its complications
  i. Glaucoma.
  ii. Open eye injury/acute globe injury.
- Severe hepatic impairment: bilirubin ≥three times upper limit of normal; Aspartate aminotransferase (AST) and/or Alanine transaminase (ALT) > five times upper limit of normal—clinically determined to be due to hepatic impairment.
- Severe renal impairment (creatinine clearance <15 mL/min by Cockroft Gault equation).
- Other mental disorders apart from major depression (lifetime history schizophrenia/bipolar/mania).
- Recent substance misuse as determined by the treating and research clinicians.

To screen for MDD in the palliative care population, PHQ-2 will be used to minimise the burden of administration to participants while maintaining a relatively high level of sensitivity and specificity.[50–52] This will be followed by a diagnostic interview using Endicott criteria. The substitute approach is to replace the four somatic items of Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria with other more depression specific items, potentially reducing the chance of misattribution of the symptoms of terminal illness as MDD.[8 53–55] Although DSM-5 is currently available, the psychometric property of Endicott criteria has not been established using DSM-5 but DSM-IV in the oncology population. As a result, Endicott criteria based on DSM-IV will be used.[56] Furthermore, the MADRS score will be performed to assess depression severity. This tool has been widely used and accepted as a standard to measure the antidepressant response of ketamine in the psychiatric literatures.[33 57–60] A usual cut-off of MADRS ≥20 indicates moderate severity depression.[33 57–60] Nonetheless, the inclusion criteria of this study have been broadened to include depression of milder severity. It is thought that ketamine may still benefit participants with milder depression when prognoses are too short for meaningful effectiveness from the typical antidepressants. Consequently, the threshold of MADRS ≥16 has been selected in this protocol to ensure participants with

clinically significant depressive symptoms are recruited, which is in congruent with Pezzella *et al*.[61]

Palliative trials of ketamine generally have a stringent set of exclusion criteria, excluding conditions commonly encountered in the palliative setting (eg, cardiac failure and intracerebral mass). The thresholds of many exclusion criteria were largely from physician's assessments rather than based on absolute values.[23–25] However, absolute thresholds for a number of these exclusion criteria have been made for reproducibility. To assimilate the clinical population who often have significant organ dysfunctions and comorbidities, efforts have been made to ensure that the exclusion criteria are relatively inclusive as shown above. Some examples include: setting a very low score of AKPS of 10 as exclusion criteria; not excluding individuals with brain metastases unless there are concurrent symptoms or signs of increased intracranial pressure; lenient exclusion criteria for systolic blood pressure and pulse rate and only excluding the severe spectrums of hepatic and renal impairments adapted from the National Cancer Institute—sponsored Organ Dysfunction Working Group[62 63] and American Society of Clinical Oncology for Anti-cancer Therapies,[64] respectively. The renal impairment exclusion has been lowered to exclude only those with a creatinine clearance of <15 mL/min, given the ultralow initial dose (0.1 mg/kg over 2 hours) of ketamine and the mild effects of its active metabolite on renal function.[65] The exclusion of ketamine use in the last 4 weeks has also been chosen as ketamine's antidepressant effect might last up to this time.[36]

Interventions

The study intervention involves the initial SC infusion of 0.1 mg/kg ketamine given over 2 hours. If there is a lack of response from the previously administered dose, further dosing escalation at 0.1 mg/kg increment on a weekly interval may be given (figure 1). Participants are allowed up to four doses (4 weeks) with the maximal dose of 0.4 mg/kg. After this treatment phase, participants are monitored for another 4 weeks to make up a total of 8 weeks as planned for the study.

The SC route of administration has been chosen as it yielded comparable efficacy to the conventional intravenous infusion and resulted in less cardiovascular, psychotomimetic and dissociative side effects.[60 66] This is possibly related to the halved peak plasma concentration

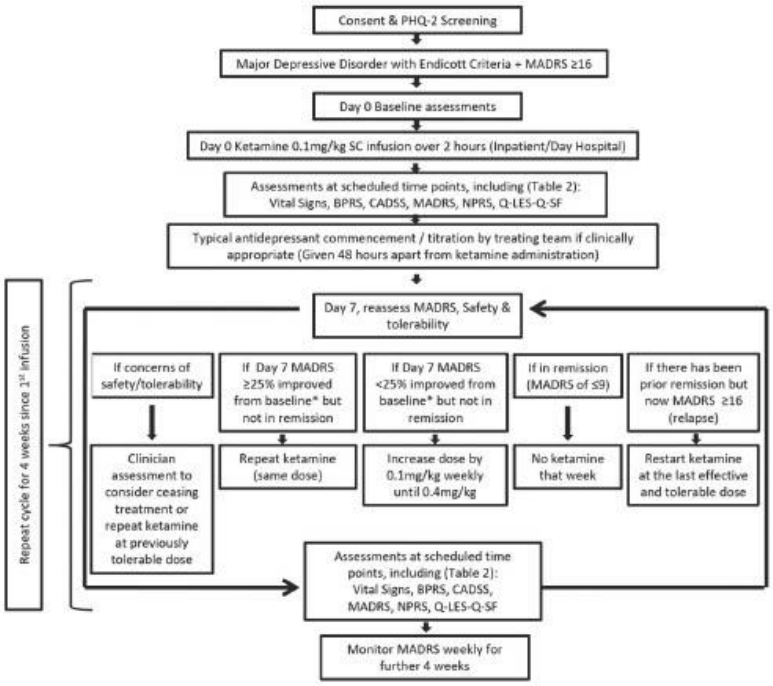

Figure 1 SKIPMDD study procedure. BPRS, Brief Psychiatric Rating Scale; CADSS, Clinician Administered Dissociative States Scale; MADRS, Montgomery-Asberg Depression Rating Scale; NPRS, Numeric Pain Rating Scale; PHQ-2, Patient Health Questionnaire-2; Q-LES-Q-SF, Quality-of-life Enjoyment and Satisfaction Questionnaire—Short Form. *Baseline MADRS score is the MADRS score prior to the last ketamine dose (default) if relapse (MADRS of ≤9) has not occurred. if relapse has occurred, the MADRS score at relapse becomes the baseline.

associated with the SC route, compared with the intravenous route.[60] The use of slow infusion subcutaneously rather than boluses may further minimise the risk of toxicity. Reports have shown that intravenous ketamine infusion over 100 mins exhibited less toxicity with comparable antidepressant effect relative to the standard infusion over 40 mins.[67 68] Additionally, the psychotomimetic effects might be spared if ketamine is commenced at ultralow dose infusion equivalent to 0.1–0.2 mg/kg/hour, even in the cancer setting.[22–24 69] Since prior studies have shown that participants' responses were observed at different dose levels even below the dose of 0.5 mg/kg, the individually tailored dose-titration approach is implemented.[59 60 66] In addition, a weekly dosing interval is scheduled as the peak response of ketamine may take up to 3 days to occur.[34 59]

After the initiation of ketamine infusion, if it is deemed appropriate for the participant's clinical needs (eg, for neuropathic pain titration), a typical antidepressant of choice at the discretion of the treating clinician can be commenced or have its dose changed 48 hours apart from the ketamine administration. There is a concern regarding the confounding antidepressant effect from allowing the introduction or dose change of the typical antidepressants during the study. However, to be in compliance with the human research ethics requirement, the enrolled participants should not be disadvantaged from the benefits of the typical antidepressants while participating in the trial, especially when the prognosis is uncertain. Furthermore, the participation does not negatively impact on their physical symptom control (eg, restricting typical antidepressants dose-titration for managing neuropathic pain or anorexia).[70 71] Given the slow onset of action of the typical antidepressant (i.e. ≥ 4 weeks),[18] and the contrasting rapid onset and offset effects of ketamine (within days), the antidepressive effect of ketamine may still be differentiated from that of the typical antidepressant.[26–35 60 67 68 72] Additionally, the minimum of 48 hours gap set between the administration of a typical antidepressant and ketamine infusion will allow for better recognition of the potential adverse effects of ketamine, which likely occur within hours of infusion with duration of less than a day.[35 60]

To determine not only short-term (<1 week) but also the medium-term responses of ketamine (1 to 8 weeks), this study includes a 4-week ketamine administration period and another 4-week follow-up period. This duration has been chosen as a balance between acquiring adequate short-term and mid-term safety and efficacy data while maintaining the study's feasibility with a potentially high attrition rate, which is expected due to the progressive nature of terminal illnesses.

Comparator

A control arm has not been included as the primary research question is feasibility—having a control arm would further lower the study feasibility.

Outcome measures

The primary outcome is feasibility, measured as absolute numbers (including accrual rate of multiple centres) and proportions of palliative care patients, who have consented, been screened for MDD, met the study eligibility criteria, treated with SC ketamine, followed up and completed the study. A priori 'stop-go' criteria for the future definitive study have been set. The use of individually tailored dose-titration SC ketamine will be worthy of further evaluation in the future definitive study if: (1) the steady-state recruitment rate is 1.25 participants per month or higher up to 24 months, but not if it is 0.5 participants per month or lower and (2) the proportion of treated participants with a positive response (≥50% reduction in MADRS score) in symptoms is 30% or higher, but not 10% or lower.

Secondary outcomes and endpoints that correspond to the secondary objectives are listed according to the various assessment time points in table 2. For measuring side effects and tolerability, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)[73] will be used to measure the general nonpsychiatric adverse events. The participating sites' familiarity with its use from running the previous ketamine trial for pain may expedite the detection of potential adverse events in this vulnerable population.[25] Nonetheless, NCI CTCAE[73] is unable to capture the psychotomimetic and dissociative symptoms of ketamine comprehensively. The standard tools of Brief Psychiatric Rating Scale (BPRS),[74 75] Clinician Administered Dissociative States Scale (CADSS)[76 77] and MADRS[78] will be used for consistency with the other available ketamine literatures in psychiatry.[30 33 60 66 79] Positive response will be defined as MADRS score reduction of ≥50% from baseline and remission as MADRS score ≤9.[35 60] Relapse is defined as MADRS ≥16 after a prior remission. The time points for MADRS measurements are chosen to capture the initial time to response (as quick as within 6 hours), the time to maximal response (usually between 1 and 3 days) and the duration of response (averaging around 7 days).[27 30–34 36 37 66] Since the MADRS depression score may be affected by uncontrolled pain, concurrent pain level will be assessed using Numeric Pain Rating Scale and correlation between these factors explored.

Time—study duration

The recruitment will occur for up to 2 years.

Study procedure

The study procedure is illustrated in figure 1. This study will be overseen and coordinated by the Australian national Palliative Care Clinical Studies Collaborative (PaCCSC) Trial Management Committee (TMC). The TMC consists of chief study investigators and key members of the PaCCSC group not involved in this study. They oversee the trial governance through PaCCSC Standard Operating Procedures, providing the trial infrastructure

Table 2 Assessment schedule

Assessments	Eligibility	Baseline (t0 min)	30 min	1 hour	1.5 hours	2 hour (infusion complete)	4 hours	6 hours	1 day	2 days	3 days	7 days	Weekly (day 7) if no repeat ketamine infusion (up to 8 weeks from initial dose)
Informed consent	X	X (Re-affirm)											
PHQ-2	X												
Endicott criteria	X												
AKPS	X	X							X	X	X	X	X
Vital signs		X	X	X	X	X	X	X					
ECG		X											
Bloods (FBC/LFT/EUC /TFT)	X												
MADRS[78]	X	X						X	X	X	X	X	X
BPRS[74 75]		X				X	X	X					
CADSS[76 77]		X				X	X	X					
NPRS[89 90]		X						X	X	X	X	X	X
Adverse Events (NCI CTCAE 4.03)[73]		X	X	X	X	X	X	X	X	X	X	X	X
Q-LES-Q-SF[89 90]		X									X	X	
Concomitant medications		X									X	X	X
SKIPMDD Participant Satisfaction Questionnaire													X (only at the end of the study—study completion or withdraw)

AKPS, Australia-modified Karnofsky Performance Scale; BPRS, Brief Psychiatric Rating Scale; CADSS, Clinician Administered Dissociative States Scale; EUC, electrolyte urea creatinine; FBC, full blood counts; LFT, liver function test; MADRS, Montgomery-Asberg Depression Rating Scale; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NPRS, Numeric Pain Rating Scale; PHQ-2, Patient Health Questionnaire-2; Q-LES-Q-SF, Quality-of-life Enjoyment and Satisfaction Questionnaire - Short Form;; SKIPMDD, subcutaneous ketamine infusion in palliative care patients with advanced life limiting illnesses for major depressive disorder; TFT, thyroid function test.

for data collection, management, analysis and monitoring processes.

Under the guidance of BD and CL (psychiatrists in the team), the coordinating principal investigator, WL, attended training by psychiatry teams to perform psychiatric assessments. WL then provides site initiation and ongoing training to the rest of the research team members (study nurse, site coordinator and investigators).

Although the screening of depression has been recommended in the palliative population due to its high prevalence,[1 3 80] screening is not yet a routine practice at participating sites. Therefore, it is an ethical requirement to obtain consent from potential participants before screening for MDD and assessing for eligibility criteria.

As patients with MDD may have impaired capacity to provide consent, research clinicians will use the MacArthur Competence Assessment Tool for Clinical Research to assess and confirm the capacity to consent.[81–83] Due to feasibility concerns for using this tool in those with significant frailty and symptom burden, rather than using the full 21-item assessment tool, the four overarching principles of the assessment tool in assessing consent capacity will be used. These are understanding; appreciation; reasoning and expressing or evidencing a choice.[81–83] Only individuals who are able to provide informed consent will be included.

Eligible participants will then undergo 4 weeks of ketamine treatment (week 1–4). During this period, the participants' responses to ketamine will be regularly monitored at a predetermined schedule (table 2). The day-7 response (MADRS score and tolerability) determines the subsequent titration of ketamine dosing (figure 1). After the initial 4 weeks, the participants then undergo the follow-up phase, in which they are monitored weekly (week 5–8). Given there is no long-term safety data of ketamine use as an antidepressant in the palliative care population, there will be no ongoing provision of ketamine for depression after the study.

Investigators will report all serious adverse events to the PaCCSC Trial Coordinating Unit, who will then liaise with the assigned medical monitor. When appropriate, the Human Research Ethics Committee will also review the safety information of ketamine. Given the feasibility nature of this study, a medical monitor rather than the data monitoring committee will be used. The investigators will stop the study if adverse event reporting indicates safety concerns.

Each participant will be allocated a unique identification number. All trial data will be recorded on the study case report forms and entered by the research nurses into Research Electronic Data Capture—a centralised electronic database protected via Secure Sockets Layer encryption.[84] All source documents and the master list linking identifying participant information and identification numbers will be stored in a locked cabinet at each site. All information will only be accessible to those who are directly involved in conducting the study. There is no anticipated sharing of data past the investigator group. Study records will be maintained for 15 years after study completion in secure archiving facilities in compliance with National Health and Medical Research Council and the Good Clinical Practice guidelines.[85 86] Data confidentiality, accuracy and protocol compliance will be monitored by members of TMC or their delegates, audited on an ad hoc basis. The study is also subjected to inspection by regulatory bodies (eg, Therapeutic Goods Administration).

Data analysis

The sample size of 32 over 2 years is projected to be an appropriate number to inform study feasibility.[87] The primary analysis will be concentrated on the feasibility metrics and adherence outcomes, which will be analysed with frequencies and percentages. The change of assessment score from baseline for side effects, tolerability and efficacy data will be analysed: percentage change for MADRS and absolute change for BPRS, CADSS, Quality-of-life Enjoyment and Satisfaction Questionnaire—Short Form and haemodynamic observations. Dependent on the nature of the data found, normally distributed data will be summarised with mean and SD and non-normal data with medians and interquartile ranges. Statistical analyses will be performed using IBM SPSS Statistics V.24.0 (IBM, Armonk, New York).

ETHICS AND DISSEMINATION

This study was approved by South Western Sydney Local Health District (reference number: HREC/18/LPOOL/466) on the 18 February 2019. Minor administrative amendments were approved on the 26 May 2020 (protocol V.1.2). Reporting of this protocol is compliant with the Standard Protocol Items: Recommendations for Interventional Trials guideline.[88] The results of this study will be submitted for publication in peer-reviewed journals and presented at relevant conferences.

Trial status

This trial has been registered in the Australian New Zealand Clinical Trial Registry, with recruitment commenced on the 29 July 2019. Due to COVID-19, this trial was suspended on 24 March 2020 and gradually recommenced with all sites recruiting on the 17 August 2020.

Patient and public involvement

There is no patient and public involvement in the protocol design.

Strengths of the current study design

This protocol's strength is that it provides key information about the feasibility of a future definitive study while exploring the safety, tolerability and efficacy of ketamine for MDD in the palliative population for up to 8 weeks. Meanwhile, the diagnosis of MDD using Endicott criteria reduces the confounding effects of the symptoms of terminal illnesses.[8 55] The use of standard psychiatry

research instruments (eg, MADRS, CADSS and BPRS) allows direct comparison of this trial with other psychiatric trials, while maintaining the use of familiar oncological and palliative care trial instruments for safety monitoring (eg, CTCAE). In particular, the use of BPRS and CADSS allows for better characterisation of the side effect of confusion caused by ketamine into various psychotomimetic and dissociative symptoms than the sole use of NCI CTCAE. Importantly, ketamine will be administered in an individually tailored dose titration design using SC infusion, likely maximising tolerability while maintaining the antidepressant efficacy.

Limitations of the current study design

This study's key limitation is its inability to inform definitive effectiveness of ketamine (not blinded RCT). Additionally, severely depressed patients who cannot consent are excluded. Due to the lack of feasibility data, the use of proxy or surrogate decision-maker for consent cannot yet be justified. Allowing typical antidepressants to be used in the study and titration of these medications for pain and other purposes due to ethical considerations may create confounding effects. However, as mentioned above, this issue may potentially be addressed by relying on the known rapidly wax-and-wane antidepressant effect of ketamine as compared with the gradual changes from typical antidepressants that take weeks to months.[13] Finally, the ketamine dose in this study is not escalated to the conventional level of 0.5 mg/kg, which has been well established for the general population with MDD due to safety /tolerability concerns.

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Competing interests CL has served on an Advisory Board for Janssen-Cilag and as a consultant for Douglas Pharmaceuticals.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement There is no anticipated sharing of data past the investigator group.

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Appendix 12. SKIPMDD protocol version 1.3

SKIPMDD Study Protocol:

Subcutaneous **K**etamine **I**nfusion in **P**alliative Care Patients with Advanced Life Limiting Illnesses for **M**ajor **D**epressive **D**isorder: A Phase II Pilot Feasibility Study

Protocol Number: 033/17

Protocol Version: V 1.3

Study Medicine: Ketamine

Study Investigators: Dr Wei Lee (Chief Principal Investigator), Dr Caitlin Sheehan, Dr Amy Chow, Dr Sungwon Chang, A/Prof Richard Chye, Prof Colleen Loo, Prof Brian Draper, Prof Meera Agar, Prof David Currow

Date of Protocol: 5th of Feb 2021

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ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse Event
AKPS	Australia-modified Karnofsky Performance Scale
AST	Aspartate Transaminase
ALT	Alanine Transaminase
AMPA	Alpha-amino-3-hydroxy-5-methyl-4isoxazeolepropionic Acid
ASCO	American Society of Clinical Oncology
BDNF	Brain Derived Neurotrophic Factor
BPRS	Brief Psychiatric Rating Scale
CADSS	The Clinician Administered Dissociative States Scale
CRF	Case Report Form
CTC	Clinical Trial Centre
CVA	Cerebrovascular Accident
DSM	Diagnostic and Statistical Manual of Mental Disorders
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HAM-D	Hamilton Rating Scale for Depression
HREC	Human Research Ethics Committees
KSET	Ketamine Side Effect Tool
MADRS	Montgomery-Asberg Depression Rating Scale
MM	Medical Monitor
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHMRC	National Health and Medical Research Council
NMDA	N-Methyl-D-Aspartate
NPRS	Numeric Pain Rating Scale
NYHA	New York Heart Association
PaCCSC	Palliative Care Clinical Studies Collaborative
PHQ-2	Patient Health Questionnaire-2
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form
SAE	Serious Adverse Event
SNRI	Serotonin-Noradrenaline Reuptake inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCA	Tricyclic Antidepressant
TCU	Trial Coordinating Unit
TGA	Therapeutic Goods Administration
TMC	Trial Management Committee
TSH	Thyroid Stimulation Hormone

CONTENTS

Lay Summary

Depression is very common in people with a terminal illness. Usual antidepressants used to treat depression can take up a few weeks to work and are not useful when life expectancy is very short, or when the depression is so severe that it needs rapid improvement of symptoms to prevent risk of harm. There is a need for treatment that helps depression sooner in these people.

Ketamine is a medication which has been widely used in anaesthetics, chronic pain and palliative care pain management. At lower doses than that used for anaesthetics and pain, ketamine has been used in otherwise well people for depression when other treatments have failed. It has been found to be fast and effective. Apart from some short-term changes in how people sense their surroundings (e.g. out of body experiences, strange sensation, unusual thoughts, disorganised thinking and possible hallucination), there were no major side effects. These transient changes can be reduced by administering ketamine under the skin rather than into a vein, and by making individual changes to the dose of ketamine needed to treat depression, starting at a very low dose and gradually increase it. However, the acceptability and effect of ketamine for depression in the palliative care setting is not clear.

This study aims to look at whether it is possible to use ketamine for depression in the setting of terminal illnesses. This will include looking at how many patients with terminal illnesses and depression want to receive ketamine, monitoring the effects of ketamine, how acceptable it is for the people receiving ketamine under the skin with the individually-tailored dosing-up method, and finding an indication of how efficacious ketamine is for depression.

Willing adult participants from palliative care services with major depression will have a medical assessment to collect relevant health information and have baseline measurements. These include questionnaires to assess mental status, regular vital signs (e.g. heart rate, blood pressure), electrocardiogram, and blood test. These measurements will be repeated at regular times throughout the study.

Participants will then receive the ketamine infusion under the skin over two hours at the lowest scheduled dose in the hospital. They will be monitored for the next six hours for any side effects and have the side effects appropriately managed if they are causing distress. Regular antidepressants can also be started by the treating doctors.

After the ketamine infusion, the participants may return to their usual residence or stay in hospital. The research team will continue to follow up the effects of ketamine at scheduled days throughout the week. Then, every week, the participants will be reassessed, and further ketamine may be given in hospital at a dose changed according to the participant's depression response. Each participant can receive a maximum of four doses of ketamine over 4 weeks, followed by a further 4 weeks of monitoring (or till the time of death if that happens earlier).

This study will help establish a new way of rapidly treating depression in palliative care patients in the setting of very limited life span for the patients, or when the severity of depression puts the patients at high risk of harming him/herself or others.

STUDY SYNOPSIS

Title	Subcutaneous ketamine infusion for major depressive disorder in palliative care patients with advanced life limiting illnesses: A phase II pilot feasibility study
Background and rationale	Depression is common in patients who have advanced life-limiting illness, significantly impacting their quality of life. There are significant time pressures for antidepressants to have rapid-onset effect in some palliative care patients. Most antidepressants, due to their slow onset of action, have limited therapeutic benefits in patients with extremely short prognoses or those with severe depression that require rapid effect while waiting for the typical antidepressants to take effect. In the psychiatry literature, subanaesthetic doses of ketamine are emerging as a novel rapid-onset antidepressant for treatment resistant major depression with high response rates, though having short-lived effect[1-15]. There has been no similar trial done using ketamine to treat even *de novo* depression in the population with advanced life-limiting illness. There is a need to explore the activity of ketamine in palliative care patients, particularly those with very limited prognosis and/or severe depression that require immediate intervention where typical antidepressants are of limited utility for depression. There is also a need to assess for ketamine's short-term (within a week) and medium-term responses (weeks to early months post ketamine administration) in these patients. Further evidence may potentially allow ketamine to be used to treat severe depression in patients with very limited but uncertain prognosis (e.g. in the range of weeks) and be considered as a bridging therapy for those who have a longer prognosis for the typical antidepressants to have effects. Trials of antidepressants in this population are difficult to conduct due to several factors, including frailty, co-morbidities, co-concomitant medications and risks of adverse effects. These factors are compounded by the anhedonia from major depression, make recruitment challenging. Prior to researchers committing to a larger phase 2/3 double blinded, cross over, randomised controlled trial, testing the activity of ketamine as antidepressant in the palliative care population, a feasibility study will be conducted to investigate: the number of patients who participate in, and subsequently complete, the ketamine intervention; the safety and tolerability of ketamine in this population; and the potential effects of ketamine on depression.
Aim	To determine the feasibility, safety, tolerability, acceptability and activity of individually tailored subcutaneous ketamine as a treatment for major depressive disorder in patients with advanced life-limiting illnesses, and to generate pilot data on ketamine's antidepressant effectiveness to inform a larger phase 3 trial

Objectives (endpoints)

To determine the:

Primary

1. Study feasibility as measured by the absolute numbers and proportions of palliative care patients, who consented, are screened for depression, meet the study eligibility criteria, are treated with subcutaneous ketamine, and complete the study with repeated weekly dosing (according to response) and assessment up to 8 weeks (to allow for assessment of medium-term response)

Secondary

2. Frequency and severity of adverse events (National Cancer Institute Common Terminology Criteria for Adverse Effect 4.0 - NCI CTCAE 4.0)
3. Frequency and severity of psychotomimetic (Brief Psychiatric Rating Scale) and dissociative symptoms (Clinician-Administered Dissociative State Scale)
4. Ketamine side effects (Ketamine Side Effect Tool – [KSET])
5. Numbers of participants with improvement in their symptoms of depression assessed with the Montgomery-Asberg Depression Rating Scale (MADRS) at measured time points over the study period
6. Pain (Numeric Pain Rating Scale - NPRS)
7. Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)
8. Reasons potential participants are unable to complete each of the stages above after consent for screening (including reasons patients are ineligible for the study).
9. Participant's satisfaction of ketamine as an antidepressant and the SKIPMDD trial process (2-item questionnaire)
10. Associations between baseline characteristics and clinical outcomes

Hypotheses

Subcutaneous ketamine, administered as a 2-hourly dose-titration infusion on a weekly basis, is a feasible, safe, acceptable, and tolerable method to rapidly reduce depression severity in palliative patients with major depression in the setting of advanced life limiting illness.

Population and setting

Patients known to the palliative care services in the acute hospital, palliative care units or in the community with advanced life limiting illness and major depressive disorder in Australia

<u>Inclusion criteria</u>

- Adult males or females known to palliative care service with age ≥18 yrs
- Palliative intent of treatment due to irreversible medical illnesses
- Patient Health Questionnaire-2 (PHQ-2) score ≥3 (Diagram 1) on screening

- Major Depressive Disorder defined by Endicott Criteria diagnosed by trained personnel (e.g. psychiatry team, psychologist or trained research team member)
- MADRS Score ≥ 16 (Depression severity score)
- Willing and able to comply with all study requirements,
- Signed, written informed consent for the study

Exclusion criteria

- Australian-modified Karnofsky Performance scale (AKPS) score ≤ 10
- Having curative intent to treatment
- Methylphenidate use in the last 4 weeks
- Changes to antidepressant doses in the last 2 weeks prior to the commencement of ketamine
- Ketamine use in the last 4 weeks
- Previous significant adverse effect or hypersensitivity to ketamine
- Concurrent phenobarbitone use
- Factors of increased risk of intracranial pressure:
  i. Recent ischaemic or haemorrhagic cerebral vascular accident in the last 1 month
  ii. Brain tumours with symptoms and signs of increased intracranial pressure
  iii. Seizure in the last 6 months
  iv. Head trauma with symptoms of increased intracranial pressure
  v. Hydrocephalus
  vi. Uncontrolled nausea, vomiting and headache (e.g. from cerebral metastases, trauma) , ≥ grade 3 nausea despite one line of antiemetics
- Factors of increased risk of sympathomimetic response (hypertension and tachycardia) with associated complications
  i. Uncontrolled hypertension with systolic blood pressure ≥ 160
  ii. Tachycardia with heart rate ≥ 120 per minute.
  iii. Symptomatic ischaemic heart disease (e.g. exertional angina) and decompensated heart failure with NYHA class III and IV symptoms
  iv. Uncontrolled hyperthyroidism (Low TSH with high T3 and/or T4)
  v. Diagnosis and history of prophyria
- Factors of increased risk of intraocular pressure with its complications
  i. Glaucoma
  ii. Open eye injury / Acute globe injury
- Severe hepatic impairment: Bilirubin ≥ 3 times upper limit of normal; AST and/or ALT > 5 times upper limit of normal - clinically determined to be due to hepatic impairment
- Severe renal impairment (Creatinine clearance <15ml/min by Cockroft Gault Equation)
- Other mental disorders apart from major depression (lifetime history schizophrenia/bipolar/mania)
- Recent substance misuse as determined by the treating and research clinicians

Interventions

Individually tailored subcutaneous infusion of ketamine, at weekly intervals by response, commencing with 0.1-0.4mg/kg over 2 hours, up to 4 doses (4 weeks) with the maximal dose of 0.4mg/kg. This is followed by 4 weeks of follow up.

Commencement and titration of a typical antidepressant for depression by the treating clinical team's choice if clinically appropriate (given 48 hours apart from ketamine administration).

Outcomes and measures

Primary Outcomes:

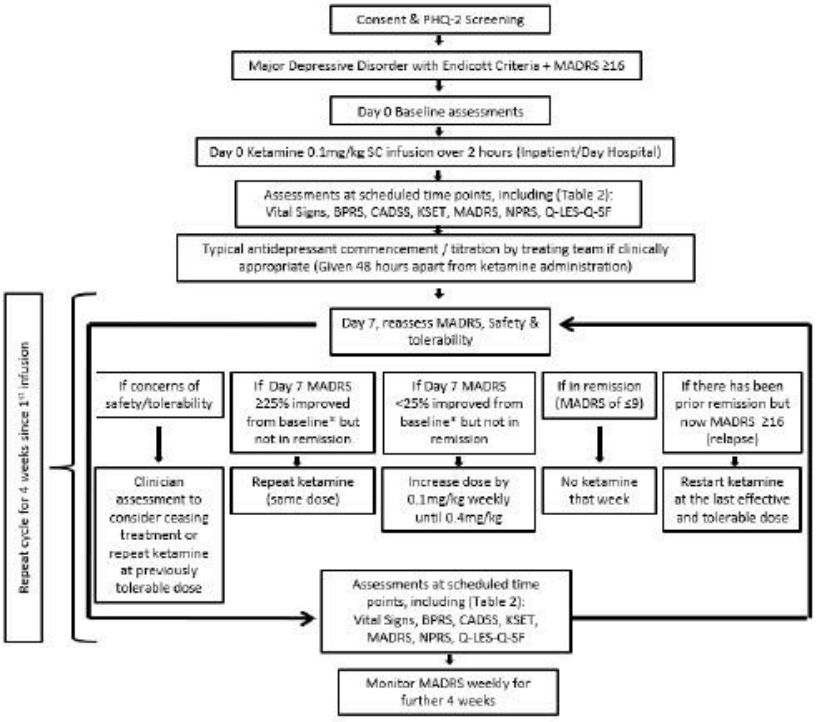
Study feasibility measures of absolute numbers (including accrual rate per month throughout multiple centres) and proportions of palliative care patients, who are consented, screened for depression, meet the study eligibility criteria, treated with subcutaneous ketamine, and complete the study with repeated weekly dosing (according to response) for 4 weeks with a further 4 weeks of follow up (A total of 8 weeks)

Secondary outcomes:

- Serious side effects (Common Terminology Criteria for Adverse Effect 4.0)
- Vital signs
- Psychotomimetic symptoms (Brief Psychiatric Rating Scale)
- Dissociative symptoms (Clinician-Administered Dissociative State Scale)
- Ketamine side effects (Ketamine Side Effect Tools – [KSET])
- Change in Montgomery-Asberg Depression Rating Scale (MADRS) (Positive response defined as reduction of ≥ 50% of the score; remission defined as score ≤9)
- Numeric Pain Rating Scale (NPRS)
- Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)
- Reasons for inability to complete each of the study stages
- Participant's satisfaction of ketamine and the SKIPMDD trial process (2-item questionnaire)
- Associations between baseline characteristics and clinical outcomes

Study procedures/ design

- Single arm
- Multicentred
- Pilot feasibility study
- Individual dose tailoring design up to 8 weeks
  - 4 weeks ketamine administration period
  - 4 weeks of follow up
- Recruitment up to 2 years



Feasibility for participating palliative care services	• Numbers of patients with major depressive disorder • Ability to screen using PHQ-2 • Availability of psychiatry input for consultation if needed • Availability of trained personnel to confirm major depressive disorder with Endicott Criteria • Ability for day admission for ketamine administration for up to 6 hours • Ability to perform vital signs/assessments (including bloods) when administrating ketamine SC infusion via SD • Ability to perform monitoring via phone follow up for up to 8 weeks per patient • Ability to recruit the required numbers within the 24 months recruitment period • Funding for the ketamine medication
Significance	Provide evidence to inform palliative physicians of the feasibility, acceptability, safety and tolerability of the use of subcutaneous infusion of ketamine in patients with advance life limiting illnesses; and allow for Phase 2/3 double blinded RCT to be performed if this pilot study proves successful to further test effectiveness.
Statistical Consideration	**Sample size estimate:** A minimum sample size of 32 over the trial period of up to 24 months is required. The use of individually tailored subcutaneous ketamine would be worthy of further evaluation in a Phase 3 study if: 1. The steady state accrual rate was 1.25 participant per month or higher up to 24 months, but not if it was 0.5 participants per month or lower. 2. The proportion of treated participants who have positive response (≥50% reduction in MADRS score) in symptoms was 30% or higher, but not 10% or lower **Statistical analysis plan** All outcomes will be reported using descriptive statistics
Risks	• Likely transient psychotomimetic and dissociative effects • Transient increase in systolic blood pressure and tachycardia • Potential risk of increasing intracranial and intra-ocular pressure • Burden on completing the study measures • Unlikely risk of over-sedation resulting in airway compromise

1. BACKGROUND

1.1 Current Challenges of Depression Treatment in Palliative Care

Depression is common in patients who have a life-limiting illness, and poses significant detrimental effects on the quality of life of those who suffer from it. The prevalence reported ranged from 13-24%[16, 17]. Depression in this population poses significant challenges due to the often uncertain but limited prognosis and the complex symptomatology that makes admission to a declared mental health facility inappropriate, even in the setting of severe depressive symptoms with risk of harm to self and others. Despite typical antidepressants (e.g. selective serotonin reuptake inhibitors and tricyclic antidepressants) being shown to be more effective than placebo in the general palliative care population, most antidepressants have limited therapeutic benefit due to the slow onset of action (at least 4 weeks)[18]. Furthermore, it may take several trials of typical antidepressants, each trial taking approximately 6 weeks, for the appropriate antidepressant that can give significant clinical benefit to be found for individual patients. Even on finding the "right" typical antidepressant, the remission rate of these typical monoamine-based antidepressants are as low as a third[19]. These have significant implications:

- Patients with an extremely short prognosis (especially those with only 1-2 weeks prognosis) will not get the benefit of the typical antidepressants, making their end-of-life care suboptimal from the untreated depression
- Patients with severe depressive symptoms and subsequent risk of harms to self and others, have a lack of therapeutic options to rapidly reverse their mood to keep them and others safe - many of these patients will not be suitable for admission in a declared mental health facility given their complex medical needs.
- Patients with a palliative diagnosis of mild to moderate depression that impact on their quality of life may need to spend a considerable proportion of the time of their remaining life to try and find the effective typical antidepressant, during which their depression continue to negatively impact on the their end-of-life planning and the subsequent quality of life of theirs and their loved ones.

There is, therefore, a need to look for therapeutic agents that have rapid onset of antidepressant action, that can act either as a sole therapy for those who have very limited prognosis or as a "bridging intervention" while waiting for the onset of the clinical benefits of typical antidepressants being tried.

Psychostimulants such as methylphenidate have been considered as alternatives to treat depression in palliative care[20-24]. However, methylphenidate's antidepressant effect may be limited for those with severe depression failing typical antidepressants, and its administration is restricted by the oral route which might not be tolerated by some palliative care patients[20, 25, 26].

1.2 Pathophysiology of Depression – A New Paradigm

There is evidence that the pathophysiology of depression cannot be accounted for solely by the lack of monoamine (serotonin/noradrenaline), as once thought, for certain subgroups of patients are refractory to the monoamine based treatment with less than a third of patients achieving remission[19]. Rather, there is evidence that depression is accounted for by the dysfunction in glutamatergic transmission[19]. In particular, there is a decrease in brain extracellular glutamate, increasing N-Methyl-D-Aspartate (NMDA) and decreasing alpha-amino-3-hydroxy-5-methyl-4isoxazolepropionic acid (AMPA) neurotransmission[27]. This has led to a lack of neural plasticity and synaptogenesis, impairing emotion and cognition[19].

1.3 Ketamine and Depression – Psychiatry Literature

Ketamine is a non-competitive NMDA receptor antagonist. Historically, it has been used predominantly for its anaesthetic and analgesic effect, even in patients with advanced life-limiting illness[28-32]. It modulates central sensitization and produces dissociation symptoms by direct action on the cortex and limbic system[33-35].

In the psychiatry literature, there is growing evidence that sub-anaesthetic doses of parenteral ketamine can act as an effective psychostimulant for those patients with treatment resistant major depression who have failed monoamine based therapy and even electroconvulsive therapy (ECT)[1-10]. It is thought that sub-anaesthetic dose of ketamine rapidly and transiently increases extracellular glutamate level in the brain. This leads to increase in alpha-amino-3-hydroxy-5-methyl-4isoxazeolepropionic acid (AMPA) receptor activation and increase BDNF brain derived neurotrophic factor (BDNF) in prefrontal cortex and hippocampus. Subsequently, there is an increase in synaptogenesis and neural plasticity, leading to the antidepressant effect[36]. Consistent with this, there is evidence that the use of ketamine improves cognitive impairment secondary to ECT[27].

Many psychiatry studies have consistently reported that low dose ketamine can induce a rapid onset of improvement in patients with depressed mood (within 2 hours of administration) and its effect can last up to one week as a single bolus dose, or up to 12 weeks as repeated boluses[2, 5-9, 36, 37]. The response rate has been as high as 70% with the number needed to treat as low as three on a meta-analysis[4, 5, 7].

In terms of tolerability and adverse effects, there have been no reported serious adverse effects in the psychiatric population who are generally younger with less co-morbidities[1, 3, 8, 9]. Many studies reported transient psychotomimetic and dissociative symptoms[1, 2, 8, 9], including some studies that showed rapid resolution of these symptoms as fast as within 2 hours of administration[8, 9], and no individuals having these symptoms beyond 4 hours[10]. Ketamine, thus, may be an effective and well tolerated agent to treat refractory major depression in an effective and fast manner.

1.4 Issues with Ketamine Trials in Palliative care

Despite the emerging evidence of the use of ketamine as antidepressant in the psychiatry population, apart from case reports of intramuscular and intravenous ketamine, open label proof-of-concept trial using oral ketamine, and a retrospective study by Iglewicz (2015) demonstrating effect of ketamine for the treatment of depression in patients receiving hospice care, there is yet a randomised controlled trial using ketamine as antidepressant to treat even *denovo* major depressive disorder in the palliative care population, particularly those with very limited prognosis and/or severe depression with risk of harm[2, 38-40].

The lack of studies of ketamine as an antidepressant in the palliative care setting may be largely contributed to the difficulty of recruitment. Recruitment might be difficult due to the terminal nature of patients' illnesses, anhedonia from depression, and the major concerns around patient's poor organ functions. Combining these factors may predispose patients to experience more adverse effects when given a ketamine dose that is commonly used in the otherwise well psychiatric population. The common intravenous route described in the psychiatric literature also makes it difficult to apply to the palliative care

setting, in part due to the preferences of patients and clinicians, as well as the lack of intensive monitoring in this setting.

Hardy et al[32] in 2012 published an article showing the lack of efficacy of ketamine for cancer pain. This, along with the psychotomimetic and dissociation side effects on giving the ketamine at analgesia dosing (much higher than the dose for depression with longer duration), sways many palliative care clinicians from administering ketamine in the palliative care population.

Given these challenges in recruitment, it is questionable whether conducting a phase 3 randomised control trial using ketamine as a rapid onset antidepressant in this population is feasible. Prior to proceeding to a phase 3 trial, a feasibility study is needed.

1.5 Possible Solution: Ultra-low Subcutaneous Ketamine Infusion with Individual Titration

Loo et al[11] in 2016 published evidence that the efficacy of subcutaneous bolus of ketamine is non-inferior to the intravenous route in treating depression, while the subcutaneous route produces better tolerability with less side effect profile than the intravenous or intramuscular routes. This, therefore, supports the use of subcutaneous route of ketamine in the palliative care population. This route is also the preferred route in many palliative care units. Additionally, Loo's study[11] is one of the first to support the effectiveness of ketamine at doses as low as 0.2mg/kg to treat major depression in the otherwise well psychiatric population, with individual titration method on repeated weekly dosing from 0.1mg/kg to 0.5mg/kg.

Meanwhile, there is, in the psychiatric population with relatively normal organ functions, evidence that increasing the duration of intravenous ketamine infusion to 100 minutes produces a similar anti-depressant efficacy with better tolerability, compared to giving intravenous ketamine in 40 minutes[12, 13]. Given the likelihood of abnormal baseline renal and liver function in the palliative population, the efficacy is likely to be maintained with an infusion over 2 hours. Acute pain literature has reported sparing of the psychotomimetic effect when the ketamine infusion was running at the equivalent of 0.15mg/kg/hr or less, which was 0.3mg/kg over 2 hours[41]. Pain literature in cancer patients has suggested that as long as ketamine is titrated gradually from a small starting dose of less than 4mg/hr (around 100mg/day), patient may not have psychotomimetic effect even when later the dose is escalated up to 12.5mg/hr (300mg/day)[29-31].

This leads to the possibility of using subcutaneous infusion of ketamine over 2 hours for depression in the palliative care population, utilising an individually tailored dose-titration approach on a weekly basis, starting from an ultra-low dosing of 0.1mg/kg, dose titrating up to produce desired effect.

Additionally, there is a need to assess for short-term response of ketamine (within a week) but also medium-term response (within weeks) of ketamine in the palliative care patients, given there is a lack of understanding around this. This would potentially allow ketamine to be used to treat depression in patients with very limited but uncertain prognosis, and even be considered as a "bridging therapy" for those whose severity of depression requires immediate intervention to prevent harm while waiting for the clinical benefits from the typical antidepressants commenced.

1.6 Current Proposal – Phase 2 Pilot Feasibility Study

This pilot study will investigate the feasibility, safety, tolerability and efficacy of ketamine for major depressive disorder in the population with advanced life limiting illness, prior to researchers committing to a larger phase 3 study. In particular, the following will be explored:

1. Recruitment feasibility demonstrated by the number of patients with advanced life limiting illness and major depression who would participate in and subsequently complete the ketamine interventions.
2. The safety, tolerability and effects of sub-anaesthetic dose of subcutaneous boluses of ketamine at doses up to 0.4mg/kg in patients with advanced life limiting illness (given the practicality of conducting the ketamine study in patients with very limited prognosis, this study will only test up to a ketamine dose of 0.4mg/kg, making it 8 weeks of total study duration)

1.7 Significance of this study

This pilot study will guide research into the feasibility of subcutaneous ketamine being used as a rapid onset antidepressant in the palliative care setting. This study will establish whether:

- Ketamine administration through this proposed study method is feasible in the palliative care units/hospitals
- Ketamine can be safe and well-tolerated by the palliative care population when given through a subcutaneous infusion as an individual-tailored titration method to minimise adverse effects
- Ketamine at subanaesthetic dose has rapid onset antidepressant activity in the palliative care population
- Future phase 3 ketamine randomised controlled trial can be feasible

As the result of this study, ketamine may be used as a novel, well-tolerated, safe and effective rapid-onset antidepressant for palliative patients with depression, either as a sole therapy for those with very limited prognosis when there is very limited therapeutic options available, or as a "bridging therapy" while patients are commenced on trials of typical monoamine based therapy. This has a significant potential to improve the palliative patients' (and their families'/loved ones') quality of life, preventing harms to patients and others as a results depression, and minimising bereavement risks.

2. AIMS, OBJECTIVES AND HYPOTHESIS

2.1 Aim

To determine the feasibility, safety, tolerability, acceptability and activity of individually tailored subcutaneous ketamine as a treatment for major depressive disorder in patients with advanced life-limiting illnesses, and to generate pilot data on ketamine's antidepressant effectiveness to inform a larger phase 3 trial.

2.2 Objectives(endpoints)

To determine the:

2.2.1 Primary

Study feasibility as measured by the absolute number of patients, who are consented and screened for depression, meet the study eligibility criteria, are treated with subcutaneous ketamine, and complete the study with repeated weekly dosing (according to response) and assessment up to 8 weeks (to allow for assessment of medium term response).

2.2.2 Secondary

- Frequency and severity of adverse events (National Cancer Institute Common Terminology Criteria for Adverse Effect 4.0 - NCI CTCAE 4.0)
- Frequency and severity of psychotomimetic (Brief Psychiatric Rating Scale) and dissociative symptoms (Clinician-Administered Dissociative State Scale)
- Numbers of participants with improvement in their symptoms of depression assessed with the Montgomery-Asberg Depression Rating Scale (MADRS) at measured time points over the study period
- Pain (Numeric Pain Rating Scale - NPRS)
- Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)
- Reasons potential participants are unable to complete each of the stages above after consent for screening (including reasons patients are ineligible for the study)
- Participant's satisfaction of ketamine as an antidepressant and the SKIPMDD trial process (2-item questionnaire)
- Associations between baseline characteristics and clinical outcomes

2.3 Hypotheses

Subcutaneous ketamine, administered as a 2-hourly dose-titration infusion on a weekly basis, is a feasible, safe, acceptable, and tolerable method to rapidly reduce depression severity in palliative patients with major depressive disorder in the setting of advanced life limiting illness.

3. STUDY DESIGN

- Single arm, multicentre, pilot feasibility study with individual dose tailoring design up to 8 weeks (4 weeks ketamine administration period and 4 weeks of follow up monitoring), for up to 2 years of recruitment.

4. SUBJECT POPULATION

Patients must meet all the inclusion criteria and none of the exclusion criteria to be eligible for this trial. There will be no exceptions made to these eligibility requirements at the time of registration. All enquiries about eligibility should be addressed by contacting the investigators listed on page 2 of the protocol or the Trial Coordinating Unit (TCU).

4.1 Target population

4.1.1 Patients known to the palliative care services in the acute hospital, palliative care units or in the community with advanced life limiting illness and major depressive disorder in Australia (inclusive of those with very limited prognosis with Australia-modified Karnofsy Performance Scale [AKPS] ≤30 and those with severe depression with MADRS ≥35)

4.2 Inclusion criteria

4.2.1 Adult males or females known to palliative care service with age ≥18-year-old
4.2.2 Palliative intent of treatment due to irreversible medical illnesses
4.2.3 Patient Health Questionnaire-2 (PHQ-2) score ≥3 (Diagram 1) on screening
4.2.4 Major Depressive Disorder defined by Endicott Criteria diagnosed by trained personnel (e.g. psychiatry team, psychologist or trained research team member)
4.2.5 MADRS Score ≥ 16 (depression severity score)
4.2.6 Willing and able to comply with all study requirements
4.2.7 Signed, written informed consent for the study

4.3 Exclusion criteria

Palliative trials of ketamine generally excluded uncontrolled hypertension, cardiac arrhythmias, cardiac failure, ischaemic heart disease, recent history of cerebral vascular accident (CVA), cerebral trauma or increased intracranial pressure, intracerebral mass, recent seizures and uncontrolled epilepsy. The thresholds of these exclusion criteria were largely physician assessed, rather than based on absolute values[30-32]. However, for reproducibility, we have made absolute thresholds for a number of these exclusion criteria.

4.3.1 Australian-modified Karnofsky Performance scale (AKPS) score ≤ 10
4.3.2 Having curative intent to treatment
- Palliative intent life prolonging measures such as target therapies, radiotherapy or intravenous antibiotics is acceptable

4.3.3 Methylphenidate use in the last 4 weeks
4.3.4 Changes to antidepressant doses in the last 2 weeks prior to the commencement of ketamine
- The interval of "2 weeks" is picked as many palliative care patients would be on antidepressant for neuropathic pain with recent dose change, and to increase the sample size. Unlike the psychiatric literature, antipsychotics are not an exclusion criterion as many palliative care patients are on these as anti-emetics)

4.3.5 Ketamine use in the last 4 weeks
- Most antidepressant effect of ketamine last for no longer than 1 month with median time to relapse of 18 days, and the 75th percentile of 27 days[36]

4.3.6 Previous significant adverse effect or hypersensitivity to ketamine

4.3.7 Concurrent phenobarbitone use - due to risk of sedation

4.3.8 Factors of increased risk of intracranial pressure

- Although traditionally there is the concern of ketamine increasing intracranial pressure, provided there is normal ventilation, ketamine may only minimally increase intracranial pressure, and even reduce intracranial pressure. The below are usually considered as relative contraindications, rather than absolute contraindications)[42-44]

4.3.8.1 Recent ischaemic or haemorrhagic cerebral vascular accident in the last 1 month

- Hardy et al's study of ketamine for refractory cancer pain did not specify the definition of "recent" CVA. However, given the likelihood of resolution of brain oedema post CVA in 1 month, this time range is chosen[32].

4.3.8.2 Brain tumours with symptoms and signs of increased intracranial pressure[42-44]

4.3.8.3 Seizure in the last 6 months

- There is evidence that seizure is not aggravated by ketamine, and that ketamine can be used to control seizure in rats[45, 46]. However, as previous seizure can increase cerebral oedema, a 6 months mark is used to ensure that there is no more significant cerebral oedema post seizure.

4.3.8.4 Head trauma with symptoms of increased intracranial pressure

- If there is no symptoms of increased intracranial pressure, then the patient is not excluded - systematic review showing that ketamine minimally increase intracranial pressure in this setting if there is no ventilation issue[43]

4.3.8.5 Hydrocephalus

4.3.8.6 Uncontrolled nausea, vomiting and headache (e.g. from cerebral metastases, trauma)

- ≥ grade 3 despite one line of antiemetics

4.3.9 Factors of increased risk of sympathomimetic response (hypertension and tachycardia) with associated complications

4.3.9.1 Uncontrolled hypertension with systolic blood pressure ≥ 160

- Ketamine IV infusion of 0.5mg/kg over 40 minutes produce a mean of 18.6mmHg increase with standard error of 2.6mmHg, which would make the patient's SBP potentially 180, which defines malignant hypertension needing intervention[47]

4.3.9.2 Tachycardia with heart rate ≥ 120 per minute.

- Ketamine IV infusion of 0.5mg/kg over 40 minutes only produce a very mild transient increase in heart rate, rarely more than 120% from baseline[10, 11, 47]. However, given the theoretical risk with clinically relevant threshold of 120/minute, this number is selected. A lower threshold is not chosen as many palliative patients have sinus tachycardia due to physiological stressors from anecdotal evidence

4.3.9.3 Symptomatic ischaemic heart disease (e.g. exertional angina) and decompensated heart failure with NYHA class III and IV symptoms

- We only exclude class III and IV symptoms as ischaemic heart disease is a relative contraindication, rather than absolute[42].

4.3.9.4 Uncontrolled hyperthyroidism (Low TSH with high T3 and/or T4)[42]

4.3.9.5 Diagnosis and history of prophyria

- Due to enhanced sympathomimetic effect by ketamine[42]

4.3.10 Factors of increased risk of intraocular pressure with its complications

4.3.10.1 Glaucoma

4.3.10.2 Open eye injury / Acute globe injury

4.3.11 Severe hepatic impairment: Bilirubin ≥ 3 times upper limit of normal; AST and/or ALT > 5 times upper limit of normal - clinically determined to be due to hepatic impairment

- This is in line with the National Cancer Institute-sponsored Organ Dysfunction Working Group, which is a classification that is well-known to the oncology clinicians. Mild to moderate hepatic dysfunctions are not excluded as many of the palliative patients will have mild to moderate hepatic impairment due to liver secondaries and other related co-morbidities[48, 49].

4.3.12 Severe renal impairment (Creatinine clearance <15ml/min by Cockroft Gault Equation)

- Recent American Society of Clinical Oncology (ASCO) recommendation validates the inclusion of mild to moderate renal impairment to creatinine clearance of 30ml/min into studies for anti-cancer therapies[50]. However, given ketamine's pharmacokinetics and its active metabolite is only mildly affected by renal function, and that the protocol is titrating ketamine from very low dose of 0.1mg/kg over 2 hours, the renal impairment exclusion is lowered to exclude those with creatinine clearance of <15ml/min[51]

4.3.13 Other mental disorders apart from major depression (lifetime history schizophrenia/bipolar/mania)

4.3.14 Recent substance misuse as determined by the treating and research clinicians

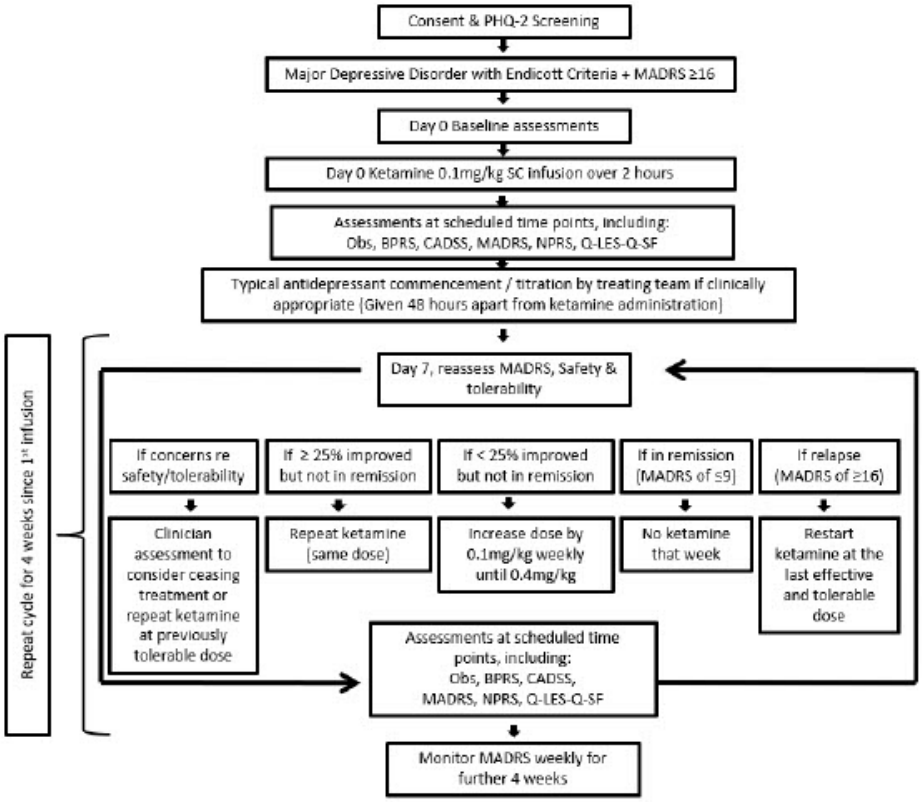
5. STUDY PROCEDURES

5.1 Summary of Procedures

1. Obtain informed consent from palliative care patients referred by treating teams (including hospital and community setting) with the clinical impression of major depressive disorder to be screened for depression with PHQ-2 and consider eligibility criteria (see exclusion criteria section 4.3).
2. Patients who are potentially eligible and score ≥3 on the PHQ-2 will then be assessed for Major Depressive Disorder (structured interview using Endicott Criteria) and depression severity score using MADRS (needs to be ≥16 to be eligible) by a psychiatrist, psychologist or a research clinician.
3. Once eligibility is confirmed and informed consent re-affirmed, the participants will proceed to baseline assessment on the day of ketamine administration.
4. Baseline assessments (including AKPS, MADRS, vital signs, BPRS, CADSS, KSET, ECG, and NPRS) are done in the inpatient or day-hospital setting on day 0 (t0min) prior to ketamine administration.
5. Medication Day 0: 0.1mg/kg subcutaneous ketamine infusion over 2 hours in the inpatient or day-hospital setting.
    a. Later, participants can be discharged or remain as inpatient according to the clinical needs after finishing the monitoring 6 hours monitoring period post ketamine commencement, the monitoring process is detailed below.
6. Monitor vital signs at t0, t30min, t1hr, t1.5hr, t2hr, t4h, t6hr post ketamine commencement
    a. Oxygen saturation by pulse oximeter
    b. Blood pressure by automatic or manual sphygmomanometer
    c. Pulse rate by clinical examination or pulse oximeter
    d. Respiratory rate by clinical examination
    e. Temperature by ear thermometer
7. Monitor BPRS/CADSS/KSET score at t0, t1hr, t2hr, t4h, t6hr post ketamine commencement
8. Monitor MADRS scores at t0min, t6 hours, t1 day, t2days, t3 days, t7 days then weekly post ketamine commencement (can be via phone post day 1)
9. Monitor NPRS at t0min, t6hr and t1day, t2 days, t3 days, t7days then weekly
10. Monitor quality of life using Q-LES-Q-SF at t0min, t3 days, and t7days (t7 days would be t0min if repeat ketamine infusion is given).
11. Assess for patient's response 1-week post ketamine infusion (safety, tolerability and response to determine subsequent dosing by the *Day 7* MADRS score [not the MADRS score during the week] as compared to the baseline MADRS score*)
    a. if in remission (defined as per psychiatric literature using MADRS of ≤9[10, 11]), there is no need for treatment that week
    b. If ≥ 25% improved but not in remission AND there is no concern around safety & tolerability, then give another treatment at same dose
    c. If < 25% improvement AND there is no concern around safety and tolerability, then increase dose by 0.1mg/kg weekly until 0.4mg/kg (assimilating the protocol by Loo et al[11])
    d. If there is concern around safety or tolerability, a clinician assessment is required to consider ceasing the ketamine treatment or repeat ketamine at a previously tolerable dose (as deemed appropriate in individual cases).

e. If relapse (MADRS score of ≥ 16) occurs, ketamine is to be restarted at the last effective and tolerable dose
f. *Baseline MADRS score is the MADRS score prior to the last ketamine dose (default) if relapse has not occurred. If relapse has occurred, use the MADRS score at relapse instead as baseline.

12. On t3-5day (48 hours apart from ketamine administration), if deemed clinically appropriate by the treating clinicians, participants can be commenced or dosed-up on a typical antidepressant (if already on one) for depression. The choice of antidepressant and whether for participants to receive it is determined by the treating clinician's discussion with the participant as per usual standard of care. The administration and monitoring of typical antidepressant adverse effects and response are all the responsibility of the usual treating clinician, not the research team. The research team will record the type, dose and timing of administration the typical antidepressant prescribed.
13. Continue ketamine intervention from point 4 to 12 for total of 4 weeks (up to 4 weekly infusions with the maximum dose of 0.4mg/kg). At any point of the ketamine administration, any concern around safety or tolerability will prompt a clinician assessment to consider ceasing the ketamine, dose reducing concurrent opioid medications, or giving appropriate interventions while continuing the ketamine administration (e.g. antipsychotic or benzodiazepine medications for distressing psychotomimetic or agitation symptoms respectively - see corresponding section 5.8).
14. Monitor MADRS and CTCAE adverse effects for the next 4 weeks (totalling 8 weeks: 4 weeks of intervention; and 4 weeks of follow-up monitoring for each participant)
15. Report relevant adverse effects throughout the study period
16. Record the number and proportion of patients who continue with the study throughout the different stages (consent, screening, eligibility, ketamine administration, and symptom monitoring period)



5.1.1 Diagram of Study Procedure

5.2 Referral process

Adult palliative care patients will be referred by their treating teams to the clinical trial team for trial consideration if the treating clinicians have the clinical impression and/or an existing diagnosis of major depressive disorder. Additionally, medical and nursing staff within each study centre will be asked to refer patients who have features of clinical depression (or an existing diagnosis) for consideration of trial entry. All research staff will be provided with a check list of inclusion /exclusion criteria with which to vet potential participants. The study nurse will ask the consultant in charge for permission to approach patients that appear to match the entry criteria. This referral will be recorded within both the Pre-screening Form and the patient clinical file. Verbal consent will be obtained from the patient and referring doctor before any medical notes are examined to check eligibility criteria.

After referral by the treating team, the potential participants will then proceed with the consent and screening processes (sections 5.3 and 5.4). For this study, given the screening method is not a routine practice of the participating palliative care units, consent is required prior to the screening process.

5.3 Consent process

Patients who appear to meet the entry requirements will be asked if they are interested in considering study entry. Those patients expressing an interest in the study will be provided with a patient information sheet approved by the research and ethics committee.

As patients with depression may have impairment in the decision-making capacity to participate in clinical research (especially in the area of appreciation of the information given), research staffs will be trained to use principles of the MacArthur Competence Assessment Tool for Clinical Research during patient encounter to confirm capacity to consent to clinical research[52-54]. MacArthur Competence Assessment Tool is for Clinical Research is chosen as it is the 21-item semi-structured interview tool that with the most empirical support, and has been validated for patients with depression[53, 54]. Due to feasibility concerns for use of this tool in those with very advanced illnesses with functional disabilities, rather than using the full 21-item assessment tool, we will use only the principles of the assessment tool in assessing capacity to consent to this trial. These principles are the 4 domains of capacity: understanding; appreciation; reasoning; and expressing or evidencing a choice[52-54]. The number of patients who were not competent to consent to this trial will be recorded. This data will be used to guide the consenting process for future phase 3 study. Proxy consent will not be used in this study, but it might be considered for the future phase 3 study.

Obtaining consent for this study will be a process of information exchange between the study staff, the potential participant and any other person the potential participant believes should be included in the discussion. The patient information sheet will be used as a basis for the discussion, and will cover all procedures (including screening & eligibility testing processes), benefits, burdens and side effects expected of possible during the study. The participant will be given opportunity (in time and physical capacity) to consider the study and formulate questions. Any questions will be addressed and answered fully. Although specified times are often recommended for consideration of consent for clinical trials, an actual time period is not specified as this will be determined in part by the patient condition. The study nurses will be trained to determine suitable time for discussion of the study against the need of the patients.

Prior to study commencement, during the site initiation visit, the study nurse, site coordinator and the investigator will be trained in consent procedures for this study, with the opportunity to role play scenarios and develop a consent script to ensure all information is fully covered.

The consent form is completed by the study nurse in accordance with the requirements of the institutional ethics committee. The form is signed and dated by the participant. The completed information sheet and consent form is copied (at the time of signing or on return to the study office)

- one copy is to be given to the patient,
- one copy is to be inserted into the medical file,
- one copy is to be filed in study file.

Throughout the study, participants are informed that can withdraw their consent anytime.

It is important to ensure that this consent process is not too burdensome for the participants, especially when they are very ill. This is particularly important as the discussions around mental health usually are more time consuming than that addressing the physical symptoms. This consenting process, therefore, is made as a one-stage consent, rather than a two-stage consent where potential participants are consented for screening and treatment separately. This also correlates with the usual investigators' practice, where explanation for the eligibility testing and the treatment are provided at the same time (as participants would ask about why the eligibility testing is done and the treatment at that same time point).

5.4 Screening & Eligibility Assessments

Consented patients will then be screened using Patient Health Questionnaire 2 (PHQ-2) (Diagram 1).

Patients who screen positive for an indication of depression (score of ≥3) will then have their mental health reviewed by their treating team. The treating team, considering the patients' individual co-morbidities and goals of care would decide on the next appropriate step of management on a case by case basis (e.g. consideration of pharmacological interventions, psychology and pastoral care input), as well as the appropriateness of formal psychiatric referral and the consideration of the ketamine trial.

Patients who agree to consider the ketamine trial will then have a structured interview by trained personnel (such as a psychiatry team member, a psychologist or a trained research team clinician) to confirm the diagnosis of major depression using Endicott Criteria (see Table 1) [55].

5.4.1 - Table 1. DSM-IV Symptoms of Major Depressive Disorder and Endicott Substitute Symptoms (Endicott Criteria) [55, 56]

DSM-IV Symptoms	Endicott Substitute Symptoms	Present: Yes/No
Depressed mood most of the day*		
Marked diminished interest or pleasure in all, or almost all, activities most of the day (Anhedonia)*		
~~Weight loss or gain (>5% body weight in a month) / change in appetite~~	Depressed appearance	
~~Insomnia or hypersomnia~~	Social withdrawal or decreased talkativeness	
Psychomotor agitation or retardation		
~~Fatigue or loss of energy~~	Brooding, self-pity or pessimism	
Feeling of worthlessness or excessive or inappropriate guilt		
~~Diminished ability to think or concentrate, indecisiveness~~	Lack of reactivity; cannot be cheered up	
Recurrent thoughts of death, or suicidal ideation or planning, or a suicide attempt		

*One of these symptoms must be present for a diagnosis of major depressive disorder. Each symptom must also meet severity criteria of "most of the day" or "nearly every day" with the duration of greater than 2 weeks. The symptoms must cause clinically significant distress or impairment and are not due to a physiological effect of medication or general medical condition. They must not be better accounted for by bereavement.

After confirming major depression by the structured interview using Endicott Criteria, the MADRS score will be performed to assess for the depression severity, and only those with a MADRS score of ≥ 16 will be able to proceed to the trial.

The inclusion criteria are broadened to include depression of mild severity (≥ 16), rather than using the usual cut off of MADRS ≥ 20 in psychiatry. It is thought that ketamine can still potentially benefit this group of participants with milder depression, as there is still a risk of their ongoing depression (though mild) significantly affecting their quality of life and negatively impact on their planning for their end-of-life care and their families.

The clinical trial nurse and an investigator will confirm eligibility (see chapter 4 for detailed inclusion and exclusion criteria), which also includes ensuring an AKPS of ≥20 and a set of bloods ruling out severe renal and hepatic impairment (blood samples within 4 weeks of study are acceptable if there is no signs of clinical deterioration).

The trial nurse will then complete the study registration process.

5.5 Registration

The participant will be assigned a subject study number at the time of referral to the study. Eligible patients must be registered before starting the study intervention. Requests for registration will only be accepted from authorised investigators at sites with ethics and site-specific approval. Registration is completed by study principal investigators or delegates filling the participant registration form after the patients having signed an informed consent form, all screening assessments have been performed and the responsible investigator has both verified the subject's eligibility. The participant registration form will include the patient identification number, site name, date eligible and date to commence intervention. Notification will be made to the National Project Officer following the completion of participant registration form.

The Ketamine infusion should be commenced as soon as possible and within 7 days of registration. If this is not possible, the relevant investigator needs to be informed for special consideration, and to ensure that the participant is still eligible for the trial when ketamine infusion can be started.

Individuals may only be registered once in this trial.

5.6 Preparation / Baseline Monitoring

Eligible patients then undergo the following baseline monitoring on the day of ketamine commencement in the hospital (as inpatient or a day hospital patient), prior to ketamine administration:

- AKPS
- Vital signs (blood pressure, heart rate, respiratory rate and oxygen saturation)
- Electrocardiogram (ECG) to rule out significant arrhythmia (e.g. Ventricular tachycardia)
- Montgomery-Asberg Depression Rating Scale (MADRS) for depression symptoms
- Brief Psychiatric Rating Scale (BPRS) for baseline psychotomimetic effects
- Clinician-Administered Dissociative State Scale (CADSS) for dissociative symptoms
- Ketamine side effects (Ketamine Side Effect Tool)
- Baseline quality of life measure using Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)
- Numerical Pain Rating Scale (NPRS)
- Any symptoms, signs or results that would be interpreted as "adverse event" once ketamine is given
- Concomitant medications must be recorded on the case report forms (CRF).

5.7 Administration of Study Treatments

5.7.1 Ketamine Infusion

Treatment intervention is an infusion dose of ketamine at the dose of 0.1-0.4mg/kg (as per section 9.2.7), drawn from a 200mg/2ml vial, mixed with normal saline up to 20ml, infused subcutaneously in a syringe driver (or equivalent) over 2 hours in the inpatient or day hospital patient setting.

A subcutaneous route is chosen as there is evidence of its non-inferior efficacy with equivalent dose of IV infusion over 40 minutes, with better tolerability[11]. The individual dose titration method of Loo et al[11] with a dose titration involving 0.1 to 0.4mg/kg is utilised to minimise intolerability and allow for early detection of toxicity, especially as the palliative population is generally frailer than the psychiatric population. Given the study aim focuses on safety and tolerability while including patients with significant organ dysfunction, rather than using the 0.2mg/kg dose where 80% or so of patients respond in the psychiatric population, we start at 0.1mg/kg infused over 2 hours[11].

Rather than a bolus, an infusion over 2 hours is used in this protocol to increase safety, acceptability and tolerability. There is evidence that IV ketamine infusion of 100min has similar anti-depressant efficacy with better tolerability than IV 40min infusion in the psychiatric population with relatively normal organ functions[12, 13]. Given the likelihood of abnormal baseline renal and liver function in the palliative population, the efficacy is likely to be maintained with an infusion over 2 hours. Acute pain literature has stated that psychotomimetic effect is spared if the infusion is running at the equivalent of 0.15mg/kg/hr or less, which is 0.3mg/kg over 2 hours[41]. Pain literature in cancer patients has suggested that as long as ketamine is titrated gradually from a small starting dose of less than 4mg/hr (around 100mg/day), patient may not have psychotomimetic effect even when later the dose is escalated up to 12.5mg/hr (300mg/day)[29-31]. Using the current protocol, the initiation dose of would be 3.5mg/hr for a 70kg man, which is less than 4mg/hr. In the palliative care setting, a dose of 0.2mg/kg/hr (equivalent of 0.4mg/kg over 2 hours) or lower, even in the setting or renal failure or liver impairment, was found to be well tolerated[57, 58]. Even if there is drowsiness or hallucination, at these rates they are mostly tolerable, and these were relieved by down titration of concurrent opioid use[29-31]. There is no set rule of the right method of opioid down titration, and it requires clinical assessment on an individual level. The appropriate rate of down titration for the individual participant should be determined by the treating clinical team. An example might be to down-titrate the total opioid dose by 25%.

5.7.2 Typical antidepressant

If clinically deemed appropriate by the treating team on discussion with the participant, a typical antidepressant of choice at the discretion of the treating clinician should be offered and commenced by the treating team. This can only be done between t3-5day (48 hours apart from ketamine infusion) to allow for better interpretation of the potential adverse effects of ketamine, distinguishing them from that of the typical antidepressant. If the participant is already on a typical antidepressant, he or she can continue it, and has his or her antidepressant dose titrated by the treating clinician to response for treating depression on t3-5day. The typical antidepressant dose can be modified during the study according to patients' need - e.g. for neuropathic pain titration. This, however, needs to be documented.

It is not the responsibility of the research team, but that of the treating clinical team, to consider the appropriateness to commence or titrate the typical antidepressants in the participant's individual situation – as this is considered as a standard of care for depression in the palliative care population. It is also the treating clinician's responsibility to determine the most appropriate method of monitoring of effects of the typical antidepressants, considering the goal of care of the individual participant, (e.g. as some participants may be reluctant to have serum sodium level checked for hyponatraemia, doing a blood test might not be clinically appropriate) like in the usual clinical care.

The typical antidepressants can include (but not limited to the below examples):

- SSRI: sertraline or citalopram
- SNRI: duloxetine, venlafaxine
- TCA: amitriptyline or nortriptyline
- Tetracyclic: mirtazapine

The research team's role is to document the type, dose and timing of administration of the typical antidepressant, and to remind the treating clinicians and participants not to commence or titrate the typical antidepressant dose within 48 hours of ketamine administration.

There is a valid concern regarding the confounding antidepressant effect with the introduction of typical antidepressant. The reason for adding in typical antidepressant in this population is to ensure that the study complies with human research ethics requirement, and that participants are not disadvantaged from the benefits of typical antidepressants while participating on the ketamine trial, especially when prognosis is uncertain.

Given the slow onset of clinical benefit of typical antidepressants, and the rapid effect of ketamine with its rapid weaning of effect after single bolus within a week in the psychiatry literature, one would be able to delineate the antidepressant effect of ketamine from the use of typical antidepressant[1-14, 18].

For participants with very limited prognosis as suggested by AKPS of 20-30 and treating team's clinical opinion, typical antidepressant is unlikely to work in time. Therefore, the use of typical antidepressant is unlikely to impact on the MADRS scoring.

For participants with good functional status and likely reflecting a longer prognosis of months with clinical benefits from typical antidepressant in the long term, but currently has severe depression with high risk of harm needing immediate intervention, typical antidepressant is added (unless contraindicated) to maximise the chance of effective treatment of depression after 4 weeks even if ketamine lacks rapid antidepressant activity. The antidepressant effect of the ketamine is likely to be able to be distinguished by its rapid onset and shorter duration of effect within 1 week, as compared to the slow antidepressant effect of typical antidepressants in 4-6 weeks.

For participants not having very limited prognosis but mild to moderate depression, if clinically indicated, there is still an ethical argument for the use of antidepressant to optimise their quality of life, especially when the prognosis of these participants is usually less than 6 months. Given there is no guaranteed response with each typical antidepressant, as it may takes a few trials, each taking up to 6 weeks of the participant's life, prior to seeing the effect of the typical antidepressants. Ketamine, from the psychiatry literature, has a higher efficacy and a more rapid onset of action than these typical antidepressants, making it potentially very useful as a "bridging therapy" until the effective typical antidepressant is found for these individuals.

5.8 Management of side effects

Adverse effects will be monitored and generally classified according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE 4.0) unless they are better classified using another

method. Participants, who experience side effects will be monitored, and reviewed with all vital signs recorded by the research team. If the side effects are deemed minor and not distressing the participants, the participants will continue with the ketamine protocol without adjustments.

All participants experiencing significant side effects, which they find distressing, will be reviewed by the treating clinicians or the research clinicians, who will decide on the most appropriate action(s). These might include ceasing the ketamine administration, if the side effects are deemed to cause significant participant harm or distress.

For minor side effects, clinicians, together with the participants, may choose to continue with the ketamine administration with the addition of other supportive measures.

The management of common or clinically significant side effects are illustrated in Table 1 below.

Psychotomimetic and dissociation symptoms are common transient side effect of ketamine, though generally well tolerated in the psychiatry population. If participants are distressed, PRN antipsychotic or PRN benzodiazepine can be used to treat distressing psychotomimetic symptoms or agitation respectively. E.g. PRN haloperidol 0.5mg Q4h and PRN midazolam 2.5mg Q2h.

If on opioids, drowsy participants may need their concurrent opioid dose reduced at a rate deemed appropriate by the treating clinician. It is important to note that the short half-lives of ketamine are short, with the alpha phase (anaesthetic phase) half-life of only 10-15 minutes, and the longer beta phase half-life in the peripheral tissue being only 2.5 hours[59]. Prolonged drowsiness from the proposed ketamine administration is, therefore, unlikely.

Those with seizure needs immediate clinician review and have ketamine ceased due to the risk of increasing intracranial pressure, worsening seizure.

Anyone with presyncope will need vital signs performed immediately and managed according to the finding. Eg. If tachycardia, follow the tachycardia pathway.

Participants who experience palpitation will require a set of observation (including blood pressure, pulse per minute, oxygen saturation, respiratory rate, temperature) and an electrocardiogram to be performed and reviewed by a clinician immediately to look for clinically significant cardiac arrhythmia and determine the next appropriate intervention and monitoring strategy.

Participants with significant hypertension (≥ systolic 180mmHg) or tachycardia (≥ 140/min pulse rate) consistently over 3 readings during 30 minutes will require cessation of the current dose of ketamine administration, have repeat vital signs for 4 hours at a frequency deemed appropriate by the research or treating clinicians (e.g. every 20 minutes). An appropriate single dose anti-hypertensive or anti-tachycardic agent may need to be considered if the blood pressure and/or heart rate remain high or symptomatic.

Ketamine, as an anaesthetic and sedative medication, poses a theoretical risk of increasing laryngeal obstruction for those with known risk of laryngeal obstruction, though it has not shown to cause respiratory compromise in the psychiatry literature using higher dose than this protocol. Anyone with symptomatic laryngeal obstruction will need a timely clinician review and has ketamine ceased.

Participants with nausea can have PRN antiemetics, which should be recorded by the research team. If the nausea is causing significant distress to participant, there needs to be a clinician review to rule out increase intracranial pressure with the have ketamine ceased if this is related to ketamine.

Participants with blurred vision and eye pain will need research staff review. Transient grade 1 visual blurring not affecting activities of daily living need monitoring by the research staff until symptom resolves. If the visual blurring persists beyond 4 hours of the ketamine infusion, or is symptomatic and impairing activities of daily living (≥Grade 2), a clinician review is required, and consideration for reducing or stopping further ketamine should be made.

Any urinary tract pain or urgency will require a clinical workup to rule out infective cystitis and other causes non-related to ketamine by clinician. If the symptoms are limiting activities of daily living (ADLs), and thought to be related to ketamine, ketamine will need to be ceased.

Local skin reaction and allergic reactions will require clinician review and consider cessation of the ketamine administration if significant and appropriate interventions instigated. This may involve antihistamine, steroid, and possibly adrenaline if severe).

Participants with existing hypernatraemia can have their hypernatraemia managed by the treating clinician as per clinician's standard of care, and continue on ketamine infusion as the current dose regimen is unlikely to cause significant symptom distress for these participants.

Table 2: Management of common or clinically significant side effects:

Symptom	Severity / Grade (CTCAE)	Treatment
Psychiatric		
Psychotomimetic symptoms/Dissociation/ Agitations	Clinically not distressing participants	• Presence of research staff with ongoing monitoring and reassurance as per study schedule
	Clinically distressing participants	• Clinician review • Clinicians to consider* • PRN midazolam 2.5mg Q2h subcut • PRN haloperidol 0.5mg Q4h subcut
Neurological		
Drowsy	Grade 1-2, or noticed but tolerated by participant	• Clinician review and reduce concurrent opioids (e.g. 25% dose reduction) • Assess for other causes of drowsiness and manage accordingly
	Prolonged, or ≥ Grade 3	• Cessation of ketamine, review of opioids, assess for other causes of altered consciousness and manage accordingly
Seizure	Any grade	• Urgent clinician review • Cessation of ketamine / stop study

		• Consider PRN Midazolam 5mg Q15minutes subcut or PRN Clonazepam 0.5mg subcut STAT* • Clinician review to assess causation and manage seizure accordingly
Cardiovascular		
Presyncope	If present – Grade 2 (e.g. near fainting)	• Vital signs and manage according to findings of vital signs. E.g. if tachycardia, assess and manage via tachycardia pathway. • Clinician review to assess causality to ketamine, and consider ketamine cessation if deemed related and clinically significant.
Palpitation		• Recording of vital signs + ECG + clinician review
	Grade 1 - mild symptoms + intervention not indicated	• Presence of research staff with ongoing monitoring and reassurance as per study schedule
	Grade 2 - intervention indicated	• Cessation of ketamine; clinical intervention as deemed appropriate by the treating clinicians
Hypertension	<Grade 4 / asymptomatic	• Presence of research staff with ongoing monitoring and reassurance as per study schedule
	Grade 4 - malignant hypertension / consistently ≥systolic 180mmHg over 3 readings in 30 minutes	• Cessation of ketamine • Clinician review • Repeat blood pressure and other vital signs in 20min intervals for 4 hours • Manage appropriately by the treating clinician with consideration of single dose antihypertensive (e.g. Prazosin 0.5mg PO STAT)*
Tachycardia	<140/min pulse rate and asymptomatic	• Presence of research staff with ongoing monitoring and reassurance as per study schedule
	Significant tachycardia (≥ 140/min pulse rate) or if symptomatic	• Cessation of ketamine • ECG + Clinician review • Repeat pulse rate and other vital signs in 20min intervals for 4 hours • Manage appropriately by the treating clinician (e.g. metoprolol 12.5mg PO STAT)*

Respiratory		
Laryngeal Obstruction	Grade 1 – asymptomatic / intervention not indicated	• Presence of research staff / clinician with ongoing monitoring as per protocol
	≥Grade 2 (symptomatic with noisy airway breathing)	• Clinician review • Cessation of ketamine / stop study • Consider dexamethasone 4mg* if related to tumour oedema causing airway obstruction
Gastrointestinal		
Nausea	Without significant distress to participant (participant's view)	• Continue ketamine • Consider PRN antiemetic subcut* e.g: o metoclopramide 10mg o cyclizine 12.5mg o haloperidol 0.5mg
	With significant distress to participant (participant's view)	• Clinician review and assessment for increase intracranial pressure if relevant • PRN antiemetic subcut* e.g: o metoclopramide 10mg o cyclizine 12.5mg o haloperidol 0.5mg o dexamethasone 4-8mg • Cessation of ketamine if nausea thought to be due to ketamine
Vomiting	Grade 1; 1-2 episodes separated by 5 min in 24 hours	• Clinician review • If there is nausea, follow the nausea pathway.
	≥Grade 2; ≥ 3 episodes separated by 5 min in 24 hours	• Clinician review • If there is nausea, follow the nausea pathway. • Cessation of ketamine if vomiting thought to be due to ketamine
Eye/ Ophthalmic		
Blurred Vision	Grade 1 – intervention not indicated, transient, not affecting ADLs	• Presence of research staff with ongoing monitoring
	≥Grade 2 – symptomatic, limiting ADLs, persisting beyond 4 hours after ketamine infusion	• Clinician review • Consider dose reducing or cessation of ketamine

Eye pain	Any grade	• Clinician review • Cessation of ketamine if thought to have increase intraocular pressure
Genitourinary		
Urinary tract pain / urgency	Any grade (present)	• Urinary analysis • Clinician review • Continue ketamine if thought not related to ketamine • If ≥grade 2 (limiting instrumental ADL) and thought to be related to ketamine, then cease ketamine
Immunological / Dermatological		
Allergic reaction	Grade 1-2	• Clinician review • Cessation of ketamine / stop study if significant • Consider antihistamine ± steroid if clinically appropriate* (e.g. loratadine 10mg PO STAT or dexamethasone 8mg subcut STAT)
	Grade ≥3 / Anaphylaxis	• Urgent clinician review • Cessation of ketamine/ stop study • Consider adrenaline (e.g. 0.3-1mg IM STAT) as clinically deemed appropriate on top of antihistamine and steroid*

*Dosages and types of recommended medications are for recommendation only, and are dependent on individual clinical assessment.

5.9 Dose Modification

Dose modification (different to the individualised "dose titration" of the proposed ketamine intervention) is not required for participants, because:

1. The patients with the highest risks of adverse events, namely decompensated heart failure of New York Heart Association Class III and IV levels, end-stage renal failure and severe liver impairment, are not included in the study.
2. To prevent toxicity, we are utilising an individual titration protocol, starting from a low dose of 0.1mg/kg over 2 hours subcutaneously (see section 5.3 above)
3. Current administration dose is at a rate that is much less than the dose and rate required for anaesthetic induction, which requires 1-4.5mg/kg given intravenously over 1 minute, giving rise to an anaesthetic effect starting in 30 seconds and lasting for 5-10 minutes. If given as intramuscular bolus at a much higher dose of 6.5-13mg/kg, the anaesthetic effect lasts 12-25 minutes[59].

5.10 Concomitant Medications/Treatments

5.10.1 Recommended

No other medications or treatments are specifically recommended in this study. However, if patients experience significant psychotomimetic or dissociation symptoms, PRN benzodiazepine and PRN antipsychotic can be offered (see section 5.8 Table 2).

5.10.2 Permitted

Typical antidepressant use is permitted, provided there is no change of dose in the 2 weeks prior to the commencement of the first dose of study medication. In fact, a typical antidepressant trial should be considered by the treating clinician if the participant is not already on it on the ketamine commencement day if clinically deemed appropriate by the treating team.

These include the following (but not limited to): SSRI (e.g. sertraline, citalopram); SNRI (e.g. duloxetine, venlafaxine), TCA (amitriptyline, nortriptyline) and tetracyclic antidepressant (mirtazapine)

Antidepressant dose, if required to be changed post the administration of ketamine, need to be recorded and the clinical trial nurse needs to be informed. Ideally, for ease of research data analysis purpose, there will be no changes to antidepressant doses during the study period of 8 weeks. However, given the potential for clinical instability of this patient population (such as changing neuropathic pain needing antidepressant dose change), as well as the ethical concern of ensuring treatment of depression using a known effective therapy for participants who might live long enough to receive its benefit, we have allowed for changes of typical antidepressant doses during the study. Any use and change of typical antidepressant will need to be accounted for and put in consideration when interpreting the antidepressant effect from ketamine. The rapid-onset nature and the rapid weaning of antidepressant effect of ketamine within a week would be used to aid investigators to differentiate the antidepressant effect from the typical antidepressants, which are slow and gradual over weeks.

Other medications that are permitted and need to be carefully documented (**doses below are examples only; the exact doses of medication required for symptom relief needs to be determined by the treating clinicians at the time of assessment**):

- Antipsychotic medications are permitted for the symptomatic treatment of nausea or distressing psychotomimetic symptoms. For example, haloperidol at a dose of 0.5mg Q4h PRN PO/IV/SC.
- Benzodiazepine:
    - Clonazepam PRN 0.25-1mg BD for neuropathic pain/insomnia/seizure control / agitation
    - Lorazepam PRN 0.5-1mg TDS for dyspnoea / anxiety / agitation
    - Midazolam PRN 2.5-5mg Q2h for agitation / dyspnoea
    - CRISIS Midazolam 5mg Q10mins PRN SC for CRISIS SOB/agitation/seizure/bleed - where patient is imminently dying in distress
- CRISIS Morphine 5mg Q10mins PRN SC for CRISIS pain/SOB - where patient is imminently dying in distress
- Antimicrobials:
    - Macrolide antibiotics (e.g., azithromycin, clarithromycin – may mildly increase ketamine effect)
    - Antifungal agents (e.g., ketoconazole, fluconazole – may increase ketamine effect)

5.10.3 Prohibited

The following medications should not be used during this study. Participants who require treatment with any of these agents will need to discontinue study treatment. Use of any of these medications during the study would require a prior discussion with the lead study investigator by contacting either the central office of the Palliative Care Clinical Studies Collaborative (PACCSC) or the investigator direct:

- Methylphenidate – known psychostimulant that can confound the depression score
- Phenobarbitone – due to its sedative effect

5.10.4 Concomitant Medication Reporting

The dose and frequency of antidepressants, as well as all the medications taken by the patients must be recorded on the day that ketamine is administered (Day 0), and then on a scheduled twice-weekly basis (Day 3, Day 7) throughout the whole study duration for the patient.

5.10.5 Compliance

Medication compliance to ketamine administration will be recorded by the study nurses at the time of the administration of the study medication to the patients on weekly intervals using the approved medication administration record within each organisation.

5.10.6 Treatment Cessation

Treatment cessation refers to *permanent* cessation of ketamine due to reasons illustrated below. Participants with treatment cessation will still have the weekly follow up including week 5-8 assessment unless they refuse to consent to it. If the participant withdraw consent for follow up while ceasing treatment, the process of "Study Withdrawal" should be followed (section 5.10.7), and the participant will withdraw from the study.

There will not be temporary ketamine cessation allowed - this is different to withholding the ketamine dose as per titration protocol due to remission and later re-starting ketamine if depression relapsed on assessment at the end of week 2 or 3 (Refer to Diagram 6.1.1 – Diagram of Study Procedure).

Study treatment will be permanently ceased for any of the following reasons, while the participant remains on the study for follow up/monitoring:

- Unacceptable toxicity or intolerance as determined by the participant or site investigator
- The site investigator determines that continuation of treatment is not in the participant's best interest.
- Participant's condition decline to AKPS ≤ 10, or deteriorated to the extent that the participant is unable to engage in an interview
- Occurrence of an exclusion criterion affecting the participant's safety, e.g. decompensated heart failure with acute pulmonary oedema or fulminate hepatic failure
- Required use of a concomitant treatment that is not permitted, as defined in section 5.10.3.
- The participant declines further study treatment

The reasons for ceasing treatment will be documented in the participant's medical record and within the study documentation ie. CRF for treatment cessation.

5.10.7 Study Withdrawal

Study withdrawal refers to participants exiting the study prematurely, withdrawing consent for treatment and monitoring. At this time, the "end of study" case report form with the SKIPMDD questionnaire and the reason(s) for study withdrawal needs to be completed.

Reasons that constitute study withdrawal include reasons for treatment cessation as described in section 5.10.6 while participants refuse further follow up, as well as failure to comply with the protocol, e.g. repeated failing to have scheduled assessments.

5.10.8 Study discontinuation

The study will be stopped if reporting of adverse events indicate that review of the study protocol is required, for either the study drug, or if the incidence and review of serious adverse events indicate a review of continuation is necessary.

5.11 Study Closure

The study will be closed to recruitment after 23 months if the requisite sample size has not been reached, and closed after 24 months subsequent to the completion of the last 4 weeks of follow-up.

5.12 Post Trial Closure Treatment

Given there is no long-term safety data of ketamine use as antidepressant in the palliative care population, there will not be provision for ongoing ketamine treatment for depression after the study.

If a participant has clinically meaningful improvement in depression, he/she will have been commenced on an antidepressant (unless contraindicated) that will hopefully be having a beneficial effect. Ongoing care of the participant's depression after trial closure will be given by the participant's treating physicians, rather than by the research team.

6. ASSESSMENT PLAN

6.1 Schedule of assessments

For each ketamine infusion, patients will be assessed as per table 2, assessment schedule below.

Table 2. Assessment Schedule.

Assessments	Eligibility	Baseline (t0 min)	30 min	1hr	1.5hr	2hr (infusion complete)	4hr	6hr	1 day	2 days	3 days	7 days	Weekly (day 7) if no repeat ketamine infusion (up to 8 weeks from initial dose)
Informed consent	X	X (Re-affirm)											
Patient Health Questionnaire PHQ-2	X												
Endicott Criteria	X												
AKPS	X	X							X	X	X	X	X
Vital Signs		X	X	X	X	X	X	X					
ECG		X											
Bloods (FBC/LFT/EUC /TFT)	X												
MADRS	X	X						X	X	X	X	X	X
BPRS		X				X	X	X					
CADSS		X				X	X	X					

Assessments	Eligibility	Baseline (t0 min)	30 min	1hr	1.5hr	2hr (infusion complete)	4hr	6hr	1 day	2 days	3 days	7 days	Weekly (day 7) if no repeat ketamine infusion (up to 8 weeks from initial dose)
KSET		X				X	X	X					
NPRS		X						X	X	X	X	X	X
Adverse Events (CTCAE 4.03)		X	X	X	X	X	X	X	X	X	X	X	X
Q-LES-Q-SF		X									X	X	
Concomitant medications		X									X	X	X
SKIPMDD Participant Satisfaction Questionnaire													X (only at the end of the study – study completion or withdraw)

6.2 Assessment Tools

Patient Health Questionnaire-2 (PHQ-2)

Patient Health Questionnaire-2 (PHQ-2) (Diagram 1 of Appendix) is a two-item questionnaire that asks the participants about the degree of anhedonia and depressed mood in the last two weeks. PHQ-2 is used in this context due to its feasibility (being only a two-item questionnaire) in palliative care patients with significant frailty and propensity for questionnaire fatigue[60, 61]. In fact, two item questionnaire is the most commonly used screening tool for depression for the Australasia palliative care physicians[62]. In the cancer and palliative setting, PHQ-2 has been shown to be more specific than the single item questionnaire, while being comparable to the well-established Patient Health Questionnaire-9 and Hospital Anxiety and Depression Scale in screening for major depression, and superior to the National Comprehensive Cancer Network Distress Thermometer[60, 63]. A cut-off score of ≥3 is taken as the optimal balance between sensitivity and specificity for screening for the palliative population, as suggested in the literature, with a sensitivity of up to 100% and specificity of up to 92%[60, 61, 63, 64].

The PHQ-2 is administered as part of the eligibility assessment, by asking the patient to respond to 2 questions and the response recorded on the approved form.

Endicott Criteria

Diagnosing major depression in patients with advanced life limiting illness is difficult due to the systemic effects (fatigue, weight loss, and anorexia) of the underlying pathophysiology of the disease patients are suffering from. These symptoms mimic the symptoms for major depression as defined by DSM IV criteria [55, 65, 66]. Despite being able to still identify patients with severe depression in terminally ill cancer setting, DSM IV criteria was found to over-identify non-depressed patients as having mild depressive symptoms in this setting[67].

Endicott criteria (Table 1 of Appendix), was a substitutive approached devised by Jean Endicott to counteract this issue[55]. It replaces four somatic items of DSM IV (poor appetite or weight loss; sleep disturbance; fatigue; and diminished concentration) with four other items that correspond to depressive symptoms - namely: tearfulness or depressed appearance; social withdrawal or decreased talkativeness; brooding, self-pity or pessimism; and reduced reactivity (cannot be cheered up, doesn't smile, no response to good news or funny situations)[55]. Endicott Criteria reduces the chance of over-identification of non-depressed patients as having mild depression, and has a higher utility of identifying depression across all severity of depression in palliative patients, as compared to DSM IV[55, 66-68].Given the current study involves diagnosing depression in the palliative population, Endicott Criteria is used for the diagnosis of major depression.

The Endicott Criteria is completed via a structured interview by trained personnel (such as a psychiatry team member, a psychologist or a trained research team clinician) to confirm the diagnosis of major depression. The outcomes are recorded on the patient's clinical record as well as the case report forms.

Montgomery-Asberg Depression Rating Scale (MADRS)

Montgomery-Asberg Depression Rating Scale (MADRS) (Diagram 2 of Appendix) is a well validated, interview based, 10-item instrument for measuring depression severity. Each item is rated from 0-6 (6 being the most severe). It was designed to further improve the sensitivity of Hamilton Rating Scale for Depression (HAM-D) in detecting response to antidepressants[69]. It has been widely used and accepted as the standard of measuring antidepressant response in the ketamine randomised control trials[4]. However, palliative care clinicians are not as familiar with MADRS as the known Hospital Anxiety and Depression scale (HADS) in assessing for depression. After extensive discussion, the investigator team has decided to proceed with the use of MADRS rather than HADS to measure response due to the following[1, 6, 20, 70-72]:

- HADS is accepted as a useful screening tool for depression in palliative care. However, it is not as useful in identifying major depression cases (particularly those with severe depression who are socially withdrawn with impaired communication), and has little evidence to support its use in determining a response to ketamine. MADRS, on the contrary, is widely accepted in the psychiatric literature to monitor depression response to ketamine.
- MADRS scale is an observer scale while HADS is based on self-report which is less objective. This makes MADRS a better scale to assess depression rather than subjective depressed mood in this setting, especially if the depression is severe.
- Despite there being the concerns of the MADRS scale having somatic items of depression that might be affected by the terminal illness, MADRS has been chosen over HADS as a primary depression measure in the palliative population as it minimises physical symptoms of depression that might artificially inflate depression scores[20]. The investigator team thought that it is worth exploring whether ketamine impacts on the somatic items. Meanwhile, sub-analysis of ketamine on the cognitive-affective non-somatic and somatic items will also be made.

For this study, we will continue to define positive response as a decrease in MADRS score by 50% from baseline and remission as MADRS score ≤ than 9, as per psychiatry literature. A reasonable MADRS cut off for mild depression is 7-19, moderate depression is 20-34, and severe depression will be defined by a MADRS of ≥35[73-76].

Brief Psychiatric Rating Scale (BPRS)

The Brief Psychiatric Rating Scale (BPRS) (Diagram 3 of Appendix) is a well validated, widely used, interview based instrument in the ketamine trials for depression to asses for psychotomimetic symptoms, as ketamine can produce transient symptoms of psychosis (psychotomimetic symptoms)[77]. These can include anxiety, disorganised thought processes, unusual though contents, and even hallucinations. It was first developed by Overall to allow for rapid assessment of changes in psychotic symptomatology, including positive, negative and affective symptoms[78, 79]. BPRS contains 18 symptom item, each ranging from 0-7 (the higher the more severe), totalling a score of 126. This scale is clinician administered.

Clinician Administered Dissociative States Scale (CADSS).

Dissociative state, or dissociation, is the commonest transient adverse effect of ketamine administration for depression[77]. It is characterised by a "strange" or "unreal" feeling, and may involve transient symptoms of amnesia, out of body experiences, derealisation and depersonalisation feelings[80].

The Clinician Assessed Dissociative Status Scale (CADSS) (Diagram 4 of Appendix) was originally designed as a 28 item scale containing both subjective and objective items that are developed to assess dissociative states at a certain time point[4, 80]. Bremner, the developer of the CADSS, then recommended against using the objective items (24-28) but only the subjective items (items 1-23) in 2014 as many patients having marked dissociative symptoms only have little or no manifestation of their experiences, and thus are less valid[80]. Furthermore, only the subjective items of CADSS are routinely used, and are well validated to assess for ketamine induced dissociative state with high internal consistency[81].This scale has been well validated and used as a standard for measuring dissociative states in the randomised controlled trials of ketamine for depression in the psychiatry literature[4]. It has been shown to have high inter-rater reliability and high internal consistency[82]. We will therefore use the CADSS with subjective items 1-23 in the current study, which also enhances feasibility. Despite it being a scale with only subjective items, the administration of the scale requires research team member to be present with the participants to guide them through the items, as recommended by Bremner, as participants with dissociative state may find it difficult to complete by themselves[80].

Modified Ketamine Side Effect Tool (KSET)

The Ketamine Side Effect Tool (KSET) is a systematic tool that is recently developed and validated for the monitoring and reporting of ketamine-related side effects[83]. It incorporates both the psychotomimetic and dissociative side effects as well as the other general physical side effects in a comprehensive yet concise manner. It has been recommended for use in both the research and clinical scenarios[83]. However, it has not been validated in the palliative care population. Due to its brevity and ease-of-use, this tool will be assessed in relation to BPRS, CADSS and NCI CTCAE in identifying ketamine-related side effects in the palliative population. This might allow for its use in the future definitive trial, replacing BRPS, CADSS and ketamine-related items in NCI CTCAE to improve the feasibility of trial design for patients. For relevance to this trial, only the specific part of KSET (page two of the KSET - Acute Treatment) is modified and used in this study (Diagram 5).

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) is a well-validated common tool used to report adverse events in oncology clinical trials[84]. It contains a standardised list of adverse events that are commonly encountered in the oncology setting, and has a standardised severity grading from 1 to 5 (the higher the number, the higher the severity). Despite not commonly used in the psychiatry population, it is commonly utilised in palliative care trials, including the previous ketamine for cancer pain trial[32]. In order to ensure rapid detection of adverse events in this vulnerable population, given the familiarity of its use and standardisation of adverse events especially from the participating units' experiences from the previous ketamine trial for pain, this tool is chosen to measure the general (non psychiatric) adverse effects of ketamine. It will be used to classify and grade the intensity of potential adverse events up to 8 weeks post initial ketamine administration.

Numeric Pain Rating Scale (NPRS)

Level of pain may influence participants' depression score. As ketamine also has analgesic properties, the current study will explore whether there is a correlation between the antidepressant response of ketamine and any potential analgesia effect perceived by the participants.

The Numeric Pain Rating Scale (NPRS) (Diagram 6 of Appendix) has been used as it is a brief and easy tool for the assessment of pain within both the clinical and research settings[85]. It has been validated in both the pain and palliative care settings[86-88]. The scale of 0 to 10 is familiar to most palliative care participants, making it simple for participants to use, and reflects common clinical assessment of pain. The participants will be asked to make three pain rating out of 10 in the past 24 hours: the pain score for the current; best; and worst pain over the past 24 hours. The mean of the 3 pain ratings will then be used to represent the overall level of pain in the last 24 hours.

Given it is not the intention of this study to prove whether ketamine reduces pain, a more comprehensive pain scale (such as Brief Pain Inventory) is not required.

Australian – modified Karnofsky Performance Status

The Australian – modified Karnofsky Performance Status (Diagram 7 of Appendix) is a validated variant of the Karnofsky Performance Status[89]. The Australian version has criteria that can be applied in either the inpatient or outpatient setting, which is more appropriate to the population seen in palliative care[89]. This objective measure has high inter-rater reliability and is sensitive to changes in function over time. A score of 0 to 100 (in increments of 10) is assigned to patients based on their ability to undertake a range of daily tasks. This functional score directly correlate with the prognosis of the participants[90]. Thus, this tool will be used in this study to assist investigators to determine patient condition and possible prognosis, together with any measurable improvements in functional status as a result of the intervention. In particular, if a participant has a AKPS <30, this indicates a very limited prognosis where typical antidepressant is very likely futile[90].

Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q-SF)

Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q-SF) (Diagram 8 of Appendix) is a 16 item questionnaire that measures various aspects of quality of life of participants. It was previously devised by Endicott to improve the sensitivity of detecting important differences in quality of life score after antidepressant treatment when other standard measures fail to detect changes[91]. It is one of the most commonly used quality of life measure in psychiatry research, and has been well validated with high internal consistency, sensitivity of 80%, and specificity of 100%[92].

The questionnaire will be provided to participants for completion at baseline, Day 3 and Day 7 post ketamine infusion. The times are chosen considering the timing required for ketamine to take effect, and the possibility of ketamine's effect wearing off in 1-week time.

Scoring of the Q-LES-Q-SF requires summing only the first 14 items of various factors of quality of life, and transforming the raw score to a percentage of maximal possible score, indicating the patient's quality of life. It also has 2 stand-alone items measuring the score to medication satisfaction and overall life satisfaction. This tool is thought to be a feasible and reliable measure for quality of life for this current study.

SKIPMDD Satisfaction Questionnaire

Participants' satisfaction of ketamine as an antidepressant, as well as the SKIPMDD trial process will be captured through an investigator designed 2-item questionnaire. The items ask participants their degree of agreeance to the two statements below:

1: "Overall, I am happy with using ketamine to treat my depression."

2: "Overall, I am happy with the processes involved with participating in this trial." (This includes the dosing and follow-up schedules)

These items will be scored numerically from 1-5, ranging from "very unhappy" to (1) to "very happy" (5).

Along with other outcome measures listed above, this questionnaire will further characterise participants experiences of using ketamine as antidepressant and participating in this trial. This tool has not been validated, but it is designed specifically for this pilot feasibility study. It is thought to be vital in providing data about participant satisfaction for this trial. As this a physically ill population, much effort has been made to reduce questionnaire burden by keeping the item number of the questionnaire low.

Vital signs

Vital signs will be monitored regularly on each day of administration for safety, and will be collected by the study team over a period of 6 hours following commencement of the infusion. Ketamine is known to cause a transient mild elevation in blood pressure of (mean of 20mmHg) and pulse rate, with the effect lasting for no more than 90 minutes after the administration[10, 77]. Vital signs that will be measured include temperature, pulse, blood pressure and respiratory rate. These will be recorded within the medical record or nursing notes.

6.3 Blood Investigations

All blood samples will be collected by the clinical staffs who have been qualified with venepuncture training, such as pathology collectors, treating clinical team members, as well as qualified research nurse/clinicians. All blood samples will be transported to the local pathology laboratories for further analysis and storage.

Full Blood Count, Renal Function, Liver Function

Eligibility blood sampling for full blood count, renal and liver functions will be required as part of the assessment for eligibility unless a sample is available from the previous four weeks and the clinical picture has not otherwise changed within that time. Haemoglobin and white cell differentials will be performed to assess for potential symptomatic anaemia and infective process that might give rise to symptoms that mimic depression through profound lethargy or hypoactive delirium. In severe hepatic and renal failure, the risks of toxicity may increase, and thus these patients are excluded from participating in the study.

6.4 Follow Up

Participants who stop the ketamine intervention will continue to be followed up with the above assessments according to the protocol, unless consent is withdrawn.

For participants lost to follow-up, the data will be treated as missing data, using multiple imputations.

6.5 On Study Completion / Withdrawal

On study completion or withdrawal, participants will be asked by members of the trial team to complete the SKIPMDD Satisfaction Questionnaire. As illustrated in section 6.2, this is a two-item questionnaire that documents how satisfied participants are with the use of ketamine as an antidepressant, as well as the trial

processes. This can be done via phone call or in person. These results will further inform the research team about the feasibility and acceptability of this trial, and guide future trial design.

7. OUTCOMES, ENDPOINTS AND OTHER MEASURES

7.1 Primary Endpoint

The primary endpoints are the absolute numbers (including accrual rate per month throughout multiple centres) and proportions of patients, who are consented and screened for depression, meet the study eligibility criteria, are treated with subcutaneous ketamine, and complete the study with repeated weekly dosing (according to response) and assessment up to 8 weeks

7.2 Secondary Endpoints

The secondary endpoints include:

1. Frequency and severity of adverse events by NCI CTCAE v4.03
2. Frequency and severity of psychotomimetic symptoms (BPRS) in the first 6 hours of ketamine commencement, measured at baseline, t2hr, t4hr, and t6hr post ketamine commencement
3. Frequency and severity of dissociative symptoms (CADSS), measured at baseline, t2hr, t4hr, t6hr post ketamine commencement
4. Frequency and severity of ketamine side effects measured by Ketamine Side Effect Tool (KSET) at baseline, t2hr, t4hr, t6hr post ketamine commencement
5. Numbers of participants with a substantial improvement in their symptoms of depression assessed with the Montgomery-Asberg Depression Rating Scale (MADRS)
    - Positive response is defined by a decrease in MADRS score by 50% from baseline; remission is defined by MADRS score ≤9)
    - Measured at time points of t 0 min, 6 hours, then 1, 3, and 7 days post each ketamine, and weekly if no repeat ketamine administration up to 8 weeks.
    - The timing of these are to capture the initial time to response (can be as quick as ≤6 hours), the time to maximal response, (usually between 1-3 days), and the duration of response, (averages around 7 days)[2, 5-9, 36, 37]
6. Numeric Pain Rating Scale (NPRS) at t0min, t6hr and t1day, t2 days, t3 days, t7days after each ketamine infusion then weekly if no repeat ketamine infusion up to 8 weeks post initial ketamine
7. Quality of life score using Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF) at baseline, t3day and t7day
8. Reasons for inability to complete each of the study stages (assessed by interview with participant in person or via phone by research team)
9. Participant's satisfaction of ketamine as an antidepressant and the SKIPMDD trial process (2-item questionnaire)
10. Associations between baseline characteristics and clinical outcomes

8 SAFETY REPORTING

8.1 Definitions

An **ADVERSE EVENT (AE)** is a negative medical occurrence that happened to a patient who has received the treatment intervention. The occurrence does not have to have a causative relationship with the given intervention, and can be an adverse medical symptom, sign, abnormal physiological testing or disease (or the worsening of it) that is associated with the administered ketamine.

Expected signs and symptoms associated with the underlying disease or palliative diagnoses will not be reported.

A **SERIOUS ADVERSE EVENT (SAE)** is defined as those AE which:

- is life-threatening at the time of the event or leads to death
- results in inpatient hospitalisation or prolonging the current hospital admission
- ends in persistent and/or significant disability or incapacity
- results in birth defect
- are likely to become serious if left untreated in the opinion of the investigator

Importantly, if the cause of the above outcomes is due to primary progression of disease, the medical occurrence is not considered as a SAE.

A **SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR)** is an unexpected SAE that is related to the ketamine administered or related to the administration device and is not listed in the information given or published about ketamine, or not to the expected extent of severity.

8.2 Reporting of Serious Adverse Events (including SUSARs)

Investigators have the responsibility to report all SAEs (including SUSARs) to the Trial Coordinating Unit (TCU). This needs to be done in one working day of the investigators becoming aware of the event using the SAE form. The SAEs need to be reported during the time of the study till up to 30 days from the end of the ketamine administration.

The TCU will provide SUSAR reports and SAE line listings to investigators for submission to Human Research Ethics Committees (HRECs) as required. The TCU will be responsible for providing reports to the Lead HREC. The investigators must notify the local HREC as required.

The study sponsor or the TCU will submit 'reportable safety events' to the TGA in Australia.

For each of the SAE, the below information will be recorded:

- Event description including classification according to NCI CTCAE
- Primary and secondary diagnoses of event (If death/hospitalisation)
- Severity / Worst Grade
- Attribution to ketamine
- Expectedness (listed in ketamine's product information)
- Action taken with study intervention (Ketamine)
- Impact of SAE (e.g. hospitalisation details)
- Outcome of SAE including end date if recovered

9. TREATMENT INFORMATION

9.1 Investigational Product Name[59]

Ingredient: Ketamine Hydrochloride

Trade name: Ketalar

9.2 Description of Investigational Product

9.2.1 Usual Use:

Anaesthetic

9.2.2 Off-label Use:

Analgesia; Complex regional pain syndrome; Status epilepticus (refractory)

9.2.3 Availability:

Vial – 200mg/2ml. Also contains benzethonium chloride. [59, 93]

9.2.4 Stability[93]:

- Vial: store below 30 Celsius. Protect from light
- Dilated solution: When diluted with an equal volume of a compatible fluid, it is stable for 24 hours at 2-8 Celsius.

9.2.5 Compatibility:

Fluids: Glucose 5%, sodium chloride 0.9%[93]

- In this study, ketamine is recommended to mix with 20ml of normal saline

9.2.6 Incompatibility[93]:

- Drugs given simultaneously at the same local subcutaneous site : frusemide, heparin sodium , insulin (short-acting), phenobarbital (phenobarbitone)

9.2.7 Administration:

- In this study, ketamine solution (mixed in 20ml of) normal saline, is infused subcutaneously over 2 hours via a syringe driver or an equivalent infuser. The ketamine ampoule of 200mg/2ml will be used, it will be prepared in the clinical ward by registered nurses following the below instructions for preparation:
    - Ketamine will be first drawn out from the vial – drawing out the whole 2 ml (200mg) from the vial
    - Mix the whole drawn ketamine of 200mg/2ml with normal saline, making up to 20ml in a syringe, creating a solution of concentration of 200mg/20ml
    - The nurse then draws up the volume of ketamine required for the participant from the mixed/diluted solution based on the calculated weight-based dose. E.g. For ketamine commencement at 0.1mg/kg, a 70kg man requires 7mg of ketamine. This is 0.7ml of the mixed solution to be drawn. (see table 3 below)
    - The drawn diluted solution is then made into a syringe driver with normal saline, totalling 20ml.
    - The syringe driver is then infused over 2 hours.

Table 3. Ketamine dose (mg) and volume (ml) by participant weight (kg)

	Ketamine dose (mg)				Ketamine volume (ml) (from 200mg/20ml mixed with normal saline)			
Participant Weight (kg)	Ketamine (Mg/kg)				Ketamine (Mg/kg)			
	0.1	0.2	0.3	0.4	0.1	0.2	0.3	0.4
30	3	6	9	12	0.3	0.6	0.9	1.2
35	3.5	7	10.5	14	0.35	0.7	1.05	1.4
40	4	8	12	16	0.4	0.8	1.2	1.6
45	4.5	9	13.5	18	0.45	0.9	1.35	1.8
50	5	10	15	20	0.5	1	1.5	2
55	5.5	11	16.5	22	0.55	1.1	1.65	2.2
60	6	12	18	24	0.6	1.2	1.8	2.4
65	6.5	13	19.5	26	0.65	1.3	1.95	2.6
70	7	14	21	28	0.7	1.4	2.1	2.8
75	7.5	15	22.5	30	0.75	1.5	2.25	3
80	8	16	24	32	0.8	1.6	2.4	3.2
85	8.5	17	25.5	34	0.85	1.7	2.55	3.4
90	9	18	27	36	0.9	1.8	2.7	3.6
95	9.5	19	28.5	38	0.95	1.9	2.85	3.8
100	10	20	30	40	1	2	3	4
105	10.5	21	31.5	42	1.05	2.1	3.15	4.2
110	11	22	33	44	1.1	2.2	3.3	4.4
115	11.5	23	34.5	46	1.15	2.3	3.45	4.6
120	12	24	36	48	1.2	2.4	3.6	4.8
125	12.5	25	37.5	50	1.25	2.5	3.75	5
130	13	26	39	52	1.3	2.6	3.9	5.2
135	13.5	27	40.5	54	1.35	2.7	4.05	5.4
140	14	28	42	56	1.4	2.8	4.2	5.6
145	14.5	29	43.5	58	1.45	2.9	4.35	5.8
150	15	30	45	60	1.5	3	4.5	6

9.2.8 Mechanism of Action[51, 94, 95]:

- Ketamine is a noncompetitive NMDA receptor antagonist that blocks glutamate.
- Other interactions: Noradrenergic and serotoninergic re-uptake pathway, cholinergic and dopamine pathways, and calcium and sodium channels.
- Produces a cataleptic-like state in which the patient is dissociated from the surrounding environment by direct action on the cortex and limbic system.
- Low (subanesthetic) doses produce analgesia, and modulate central sensitization, hyperalgesia and opioid tolerance.
- Subanaesthetic dose of ketamine, but not at anaesthetic dose, transiently (<2hours) increases extracellular glutamate level in the brain, leading to an increase in alpha-amino-3-hydroxy-5-methyl-4isoxazeolepropionic acid (AMPA) receptor activation and an increase brain derived neurotrophic factor (BDNF) in prefrontal cortex and hippocampus. This increases synaptogenesis and neural plasticity, leading to the antidepressant effect[36]

9.2.9 Pharmacodynamics & Pharmacokinetics

Onset of action:

Anaesthetic effect: Unlikely to occur as dosage used of 0.1-0.4mg/kg over 2 hours is far lower than the induction dose and rate of 1-4.5mg/kg over 1 minute intravenously for anaesthetic action. If given IV, the onset of action of anaesthetic effect is within 30 seconds[36, 59].

Antidepressant effect: within 1 day (even within 2 hours)[36]

Duration:

Anaesthetic effect: 5 to 10 minutes; Recovery: 1 to 2 hours[36, 59]

Antidepressant effect: up to 7 days (Single dose)[36]

Distribution: V_{dss}: 1-3 L/kg[59, 96]

Protein binding: 12-50%[59, 96]

Metabolism: Extensive hepatic metabolism via CYP3A4 to norketamine, which is 1/6 to 1/3 as potent as anaesthetic, but equipotent as analgesia[59, 96, 97]

Half-life elimination: Alpha half life: 10 to 15 minutes (alpha phase is the first phase with anaesthetic action that is terminated by redistribution from the central nervous system to peripheral tissues and hepatic biotransformation to an active metabolite, lasting for 45minutes); Beta half life: 2.5 hours[59]

Excretion: Urinarywith 90% as conjugates of hydroxylated metabolites, 2-4% unchanged; 5% faecal excretion[59]

9.2.10 Adverse Reactions:

There are side effects known to be associated with ketamine. These are described in the product information and other published literature[5, 11, 59, 77, 82, 97-99]. Many of the significant adverse reactions listed are from the setting of ketamine overdose, giving ketamine through intravenous route, in the setting of ketamine abuse[5, 99]. As ketamine is administered at an ultra-low dose with a slow subcutaneous infusion and individual dose titration, the risk and severity of many of the listed adverse reactions are minimised[11]. Most of the side effects seen in the other studies using ketamine for depression are only short lived, lasting for no more than 4 hours after the dose of the ketamine, and are usually mild and acceptable to participants (listed in the table below)[10, 11].

The **management of the common or clinically significant adverse reactions** are described in section 5.8, listed according to severity and CTCAE grading where relevant (See **Table 1 in section 5.8**).

Table 3: Common adverse effect from ketamine for depression[10, 11]:

Adverse Effect	Frequency (%)	Severity /Duration
Psychotomimetic / Dissociation symptoms	12	Mild / <4 hour
Increase in blood pressure	30	Mild (around 20mmHg increase) /< 1 hour
Increase in heart rate	30	Mild / (< 120% increase) <1 hour[11]
Headache	9	Mild / <4 hours[5]
Drowsy	15	Mild / <4 hours
Dizziness	14	Moderate (most were dizzy on standing) / <4 hours
Slurred speech	9	Mild / <4 hours
Poor concentration	9	Mild / <4 hours
Poor coordination / unsteadiness	14	Mild / <4 hours
Blurred vision	12	Mild / <4 hours
Dry mouth	9	Mild / <4 hours

Table 4: Adverse Effect of Ketamine by System:

Organ System	***Adverse Effects***

Neuropsychiatric	• Hallucination
	• Delirium
	• Transient psychotomimetic symptoms[77]
	• Transient dissociative symptoms[82]
	  ○ Gaps in memory not due to ordinary forgetting (amnesia)
	  ○ Out of body experiences and distortions of sense of one's own body (depersonalisation)
	  ○ Visual perception distortion (e.g. seeing things as if they are in a tunnel / seeing things in black and white - derealisation)
	  ○ Fragmentation of the sense of self (identity disturbance)

Nervous system	• Cognitive disturbance • Concentration impairment • Memory impairment • Depressed level of consciousness • Dizziness • Spasticity • Symptoms of increase intracranial pressure (Headache, central nausea)
Cardiac	• Postural presyncope / syncope • Palpitations • Hypertension • Cardiac arrhythmia
Gastrointestinal	• Nausea and vomiting • Sialorrhoea
Dermatological	• Inflammation and/or painful rash at injection site
Respiratory	• Laryngeal obstruction/ Laryngospasm • Stridor

	• Apnoea • Hypoxia • Respiratory depression
Immunological	• Allergic reaction • Anaphylaxis
Genitourinary	• Urinary urgency, pain and frequency
Endocrinological	• Hypernatraemia (Central diabetes insipidus)
Opthalmic:	• Diplopia • Increase intraocular pressure / Glaucoma • Visual blurring

10. STATISTICAL CONSIDERATIONS

10.1 Sample Size Estimate

The sample size of 32 is deemed appropriate for the current phase 2 pilot feasibility study. This number is supported by Lancaster et al[100] when writing about the sample size required for pilot feasibility study. They recommended a sample size of 30 patients or greater to assess recruitment rate and estimate a desired parameter (e.g. effect size of ketamine), using a conservative one-sided confidence interval of 80%. This number is also supported by Cocks & Torgerson[101]: assuming a very conservative ketamine effect size/positive response rate of 30% for the future definitive trial (the number that is comparable to that of the typical antidepressants), the pilot sample size of 32 will not only help assess the recruitment rate but also obtain the estimate of treatment effect. Again, this utilises a one-sided 80% confidence interval, where if the estimate of treatment effect is not above zero, then the phase 3 definitive trial should not be proceeded. The 80% interval, as explained by Cocks & Torgerson[101], would likely satisfy the need for reasonable certainty to ensure that the treatment produces enough effect to proceed to the phase 3 trial, while keeping the trial small enough to be performed with the limited time and financial resources.

Thus, the use of individually tailored subcutaneous ketamine would be worthy of further evaluation in Phase 3 study if:

- The steady state accrual rate was 1.25 participant per month or higher up to 24 months, but not if it was 0.5 participants per month or lower.
- The proportion of treated participants who have positive response (⩾50% reduction in MADRS score) in symptoms was 30% or higher, but not 10% or lower.

10.2 Statistical Analysis

Outcomes will be analysed using descriptive statistics. The prevalence of participants with positive response and remission on the MADRS score will be further stratified by various participant characteristics, including low AKPS score of ≤30 with clinical opinion of prognosis of days to weeks and high MADRS score of ≥ 35 (to reflect severe depression)[73-76]. A one sample proportion Z test and 95% confidence interval will be performed to assess for ketamine activity.

11 STUDY COMMITTEES

11.1 Trial Management Committee

This study will be overseen and coordinated by the Trial Management Committee (TMC), which will consist of the chief investigators, and the key members of the PACCSC group.

Each meeting of the Trial Management Committee will receive from the coordinating centre a summary report of the adverse events reported by the investigators. Each summary report will be generated from the on-line entry of adverse event reports by PaCCSC sites. This summary report will be reviewed for reporting compliance, trends in events, and outstanding events that require specific attention. All TMC discussions will have minutes documented, with actions detailed, and reviewed at the subsequent meeting. The chairperson's report to the Scientific Committee will contain a summary of the discussions of the adverse event report and the agreed outcomes. The TMC will not have access to unblinded reports of adverse events.

The TMC will also closely monitor and discuss issues and rates of consent, recruitment, completion and other progress key performance indices.

11.2 Medical Monitor (MM)

PaCCSC will assign a medical monitor (MM) to review and evaluate information relevant to the safety of the investigational product used in the pilot. The MM has the responsibility to review and evaluate information relevant to the product safety throughout the implementation of the protocol at all participating sites.

The MM will be responsible for providing safety oversight and reviewing the protocol and information about the study product as it becomes available. The MM, in consultation with the investigator team and the PaCCSC national project office will provide safety review during the execution of this study. This oversight includes reviewing safety information and providing applicable recommendations. The MM will provide recommendations, as appropriate, to members of the study and investigator team. This data and safety review facilitate early detection of safety signals and maximises the chances for continued appropriateness of the research and protection of human participants.

Based on a synthesis of this information, the MM will provide appropriate recommendations to the sponsor, PaCCSC central coordinating office, participating recruiting sites and approving HRECS.

12 ADMINISTRATIVE ASPECTS

12.1 Ethics and Regulatory Compliance

This study will be performed in accordance to the following:

- Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments[102]
- NHMRC Statement on Ethical Conduct in Human Research 2007 (Updated 2018)[103]
- NHMRC Australian Code for the Responsible Conduct of Research[104]
- World Medical Assembly in the Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants[105]

Patient recruitment will only be commenced upon receiving all the necessary approvals with the documented informed consents from participants. Investigators will comply with the protocol, except when it is necessary to remove immediate hazard to the participants. In this situation the principal investigators and, HREC and TCU will be informed immediately.

12.2 Confidentiality

All data obtained in this study will be kept confidential, in accordance with Privacy Regulations (Australian Federal Register of Legislation, 2013)[106]. Participants will be each allocated a unique identification number. The data, but not including the participant identification, will be gathered from the different participating sites, and securely stored via an online central database in TCU. The master list linking identifying participant information and identification number will be stored in a locked cabinet, separate from the participant database. All information will only be accessible to those who are directly involved in conducting the study and who have agreed to compliance with the Confidentiality Agreement. The information is held for the purpose of possible future reference if the participants decide to discontinue or are unable to continue with the study. By signing the informed consent forms, the participants allow the trial staffs to access their medical records for information relevant to the study. Data will only be analysed using identification number only.

12.3 Protocol Amendments

Any change to the protocol must only be made by the Trial Management Committee, with the possible need of changing the consent form and the approval by HREC prior to implementing the change. The only exception is when it is necessary for the elimination of immediate hazards to the participants.

12.4 Data Collection

Data will be sourced from the following:

Measure	Source	Completed by
General Demographic details	Clinical file	Study nurse
General Medical information	Clinical file	Medical officer
Concurrent medications	Clinical file	Study nurse/Medical officer
Pathology results	Pathology report/database	Pathologist
Vital signs	Clinical file/CRF	Study nurse/ward records
ECG	Clinical file	Study nurse
MADRS	Questionnaire	Study nurse/Medical officer
BPRS	Questionnaire	Study nurse/Medical officer

CADSS	Questionnaire	Study nurse/Medical officer
KSET	Questionnaire	Study nurse/Medical officer
NPRS	Scale	Study nurse/Medical officer
CTCAE 4.03	Scale/ CRF	Study nurse/Medical officer
Q-LES-Q-SF	Questionnaire	Participant

12.5 Data Handling and Record Keeping

All trial data gathered must be recorded on the case report forms (CRF) with all the essential fields completed, and entered into a central electronic database (REDCAP). REDCap is a secure web-based software system for managing data in research studies. It provides user-friendly web-based CRFs, real-time data entry validation, audit trails and non-identified data export to common statistical packages. All web-based transmissions in REDCap are protected via Secure Sockets Layer (SSL) encryption. All users are given individual system usernames and passwords.

Data corrections will be done according to the instructions by the Trial Management Committee. The accuracy of the data entry will be monitored by investigators electronically signing the case report forms on entry into the database. All source documents must be kept by the investigational sites.

During the trial, the below information should be entered into the participant's medical record:

- Participant's name, contact information, and the subject number
- The date that the subject entered the study
- Evidence of informed consent (signing of the form)
- Relevant medical history
- Monitored results / trial outcome with the date and time
- Occurrence and status of any adverse events
- The date and time of the subject completing or discontinuing the study (with the reasons)

Estimated time of retention of personal information and planned disposal

Records from the study will be maintained for 15 years after study completion in secure archiving facilities. Once the 15-year waiting period is completed, the files will be erased from the database hard-drive and any paper copy shredded, including the master list linking participant name and treatment number.

The data will be retained in accordance with good clinical practice in compliance with the NHMRC National Statement and the GCP guidelines, and in a form that is at least as secure as the sources from which it was obtained.

12.6 Study Monitoring

Study data with its accuracy, and protocol compliance will be monitored by members of the Trial Management Committee or their delegates. Monitoring may include review of CRFs, patient's clinical records, and being onsite to monitor protocol compliance and perform other relevant procedures.

12.7 Audit and Inspection

The study is subject to audit and/or inspection by delegates of the PACCSC group or the Trial Management Committee, or staffs of regulatory bodies (e.g. Therapeutic Goods Administration (TGA)).

12.8 Publication Policy

Trial data will be drafted by the investigator team, and the manuscript(s) submitted to peer-reviewed journal(s) after approval of authors. PaCCSC has a publication Standard Operating Procedure which conforms to the international requirements for authorship, this will be adhered to.

12.9 Future Data Use

The data collected from this pilot feasibility study may contribute to larger future studies in this area of study by the same research team. This will be assessed once the results of this feasibility study are known. The participant informed consent form will include this to ensure informed consent are obtained. There is no anticipated sharing of this data past the investigator group and to any future investigator group on a follow-up protocol.

13. ETHICAL CONSIDERATIONS

13.1 Significance of This Study

Currently, there is a need for an effective rapid onset antidepressant that bypasses the oral route in the setting of palliative care patients with major depression. This is especially important in the settings where there is a significant time pressure for a timely effective antidepressant: for those with very limited prognosis where the typical antidepressants will not have time to take effect; and those with severe depression with risk of harm to self and others that necessitate immediate antidepressant effect prior to the effects of the typical antidepressant takes place. In the palliative care setting, given the limited prognosis, and the negative impacts of sub-optimally treated depression on patients and family members/loved ones, there is less room for ineffective antidepressant in the short timeframe than in the general psychiatry population.

This pilot study will guide research into the feasibility of subcutaneous ketamine being used as a rapid onset antidepressant in the palliative care setting. In particular, this study will establish whether:

- Ketamine can be safe and well-tolerated by the palliative care population when given through a subcutaneous infusion as a individual-tailored titration method to minimise adverse effects
- Ketamine at subanaesthetic dose has rapid onset antidepressant activity in the palliative care population
- Ketamine administration through this proposed study method is feasible in the palliative care units/hospitals
- Future phase 3 ketamine randomised controlled trial can be feasible

As the result of this study, there may be a novel, well-tolerated, safe and effective rapid-onset antidepressant that can be used for palliative care patients with depression, enabling them to engage in psychotherapy and advance care planning, improving their (and their families'/loved ones') quality of life, preventing harms to patients and others as a results depression, and minimising bereavement risks.

13.2 The Possibility of Physical Stress or Discomfort

Every study measure has been carefully chosen to ensure they provide the best possible data with the least impact and burden on the patient, and has been validated. As much as possible, the chosen study measures are non-invasive and concise (if questionnaire) in order to minimize physical stress.

The only invasive test would be the blood sample required for eligibility testing to ensure participant's safety. The physical distress/discomfort from the blood test will be short term. A blood test is not necessary if there is a blood sample already available in the previous four weeks and the clinical picture has not otherwise changed within that time.

The study protocol is carefully planned to ensure that each participant's symptoms and side effects are monitored and responded in a timely manner with clinicians assessing and instituting appropriate management strategies, giving symptom-control medications currently used in clinical practice as deemed necessary for comfort and safety. The specific potential physical side effects with associated management plan have been detailed in section 5.5 - "Management of side effect".

To minimise the chance of physical adverse effects, this study has chosen a subcutaneous infusion route, which has shown to be the most predictable and best tolerated route[11, 15, 77]. Accounting for how ill these

participants are (with organ dysfunctions and subsequent impaired ketamine metabolism and clearance), not only have we set specific exclusion criteria, more rigorous than the previous ketamine for cancer pain trial[32], we will using Loo's individual dose titration method[11], which starts with a very low dose of ketamine of 0.1mg/kg and titrate up to effect to a maximum of only 0.4mg/kg according to participants' tolerance and response. This contrasts with the conventional ketamine dose of 0.5mg/kg dose in the psychiatry literature. Through modifying the route from intravenous to a subcutaneous ketamine infusion method, the risk of any injection site reaction and transient cardiovascular side effects (< 90 minutes duration)[10] experienced by the participants are even lower[11].

Extensive effort has been made to ensure participant safety and minimise physical discomfort for them. Harms will be carefully monitored, and any discomfort responded in a timely manner.

13.3 The Possibility of Psychological Stress or Discomfort

There was a concern about whether ketamine, like other typical antidepressant, transiently increase suicidality prior to the improvement in the mood of depression. Not only is there no explicit linkage between ketamine administration causing increased suicidality[77], ketamine has been shown to reduce suicidality in as fast as 40 minutes in a systematic review, and continue to reduce suicidality severity score significant in the 3 days post ketamine use[15].

Participants may experience transient psychotomimetic symptoms. These, however, are found to be mild in a systematic review when given intravenously over 40 minutes, and are not found to persist beyond 4 hours post infusion[10]. Given we are using a 2-hour subcutaneous infusion and starting an ultra-low dose, the risk of psychotomimetic symptoms is even lower.

Some participants may experience stress associated with completing some of the study measures or while being assessed clinically, as the assessment of items associated with depression severity score include sensitive topics (e.g. suicidal thoughts). This is a vulnerable population, where reflections on participants' mental health and aspects of quality of life (such as social and family relationship, and ability to function in life) during completing study measures may cause psychological distress.

Emotional distress caused by completing the study measures will be dealt with by members of the palliative care multidisciplinary team (including clinicians, pastoral care workers, social workers, and psychologists) who would be involved either directly with the care of the participants. If the emotional distress remains significant, the treating palliative care team would consult the mental health team / local psychiatry team for further input. In the interim, the study medication (ketamine) and the typical antidepressant that has been started (if not considered clinically inappropriate) would likely aid decrease the participants' risk of harm due to major depression.

Although there may be acute psychological distress from completing these study measures, it helps raise the treating clinicians the awareness of the participants' underlying depression severity with the associated risks of harm. This allows urgent interventions to be put in place to minimise harm and ensure safety of the participants, and may create avenues for open discussion between participants and their loved ones facilitated by the palliative care team, promoting quality end of life care.

There will be no deception of participants in this study. Each patient interaction will be undertaken by carefully selected and trained study staff. This training will initially be undertaken in conjunction with psychiatrists involved in the research team, investigators and senior research personnel, who have been trained in Good Clinical Practice. This is to ensure that staffs are able to detect and monitor patient distress. Ongoing site monitoring will provide ongoing training opportunities.

13.4 Disclosure of Sensitive Personal Information

The patients will be allocated a unique identification number. The master list linking identifying patient information and ID number will be maintained in a locked cabinet, separate from the patient database, and held at each participating site. The patient database will be stored on a password-protected hard drive maintained by the study investigators. Data will be analysed by identification number only.

13.5 Exposure of Illegal Activity

It is known for patients at the end of life to seek out treatments that offer potential assistance in the management of distressing symptoms, including the use of medications and treatments that are not approved for use, and may be illegal. All study staff are trained to discuss very sensitive and personal issues raised in discussion during participation in clinical trials and how to discuss any issues raised with the patient and or refer to the clinical team if appropriate. This study does not anticipate the recruitment of those directly involved in illegal activity, identification of such will be co-incidental and no greater than usually exists in this population.

13.6 Economic Harm

There is no anticipated financial or economic harm anticipated from this study, apart from what might be incurred from participants travelling to and from hospital if they are not inpatients.

13.7 Discrimination, Stigma or Other Social Harm

Being diagnosed with major depression during the stay might be associated with certain stigma and being seen as "weak". However, not diagnosing and managing the underlying masked depressive symptoms which may pose great risk of self-harm and harm to others would lead to much extensive social harm.

Ketamine, like several other palliative care medications (E.g. opioids), is known to be drug of abuse potential. Participants on the trial may feel anxious about being stigmatised as a "drug user". The study intervention (ketamine) will be administered only within a hospital environment. No medication will be provided to take home. Thus, this minimises the anticipated risks of social harm and discrimination associated with ketamine use.

13.8 The Possibility of Familial Distress

Members of the participants' family might be distressed on knowing the diagnosis of major depression of the participants. As with the possibility of psychological distress of the participants (see section 13.3), this study would help unmask underlying issue of major depression of participants, and allow for urgent intervention to prevent further harm to participants and their loved ones caused by depression. Any familial distress will be managed by the palliative care multidisciplinary team (including pastoral care workers, social workers and psychologists), whose members are very well trained to recognise and manage distress in the family.

13.9 Harm to Any Member of A Vulnerable Population

Palliative care patients with major depression are vulnerable population. The study aims and design are aimed towards reducing harm in this very vulnerable population. Depression is a real and often under-recognised clinical problem, and if very difficult to treat in patients where the usual medications are unlikely to have a clinical effect. This study attempts to explore another treatment option.

There are many distressing symptoms faced by participants with a life limiting illness and there is very little research to support many of the interventions provided on a daily basis. Although establishing a research using ketamine in participants towards the end of their lives poses ethical challenges, not conducting research into the best management of the these participants to promote their mental wellbeing and quality of life would likely lead to more harm. Importantly, participants will be cared for as individuals with specific needs; the needs of research will come second.

Research staff (medical, nursing, or psychologists) will clearly identify themselves and the purpose of their visit at their contact with the participants communicated as part of the research process. Training during the site initiation visit will allow research staff to determine the most appropriate methods of managing various clinical scenarios that might arise during their research visits to optimise patient care for the participants.

13.10 Research On people In Dependent Relationships

Participants of the study may feel that they are in a dependent position in this doctor-participant relationship, thus feel pressured to continue with the trial. The research team will work to minimise any possibility of undue influences. For example, the study will be presented to the potential participants by the palliative care service and the research team as unbiased as possible, separating the usual clinical care from the research tasks. A research personnel not directly involved in the clinical care of the participant will acquire informed consent, which will be re-affirmed prior to the commencement of ketamine administration. The information sheet and consent forms will be easy-to-read and clear. Participants will be regularly informed that they are able to withdraw from the study at any time, not having their clinical care affected.

13.11 Driving Safety

Ketamine is an anaesthetic agent, which poses a theoretical risk of sedation and altered level of consciousness, making driving unsafe. Although using a subanaesthetic dosage of ketamine over a short time, with a short alpha half life of 10-15minutes (the phase that has its central nervous system action prior to redistribution to the peripheral tissue), makes it unlikely for participants to remain with altered consciousness after 4 hours post infusion, participants are prohibited to drive for potential concerns around safety on the day of receiving ketamine.

13.12 The Possibility of Psychological Distress of Researchers

Research team members who have direct contact with depressed participants may feel a sense of powerlessness and hopelessness. Prior to participant contacts, all research team members will have relevant mental health training through the psychiatrists in the research team, and be made aware of available resources if they experience psychological distress. There will be regular "team debriefing sessions" to ensure that research team members are well supported. If there is significant distress from a research team member, the research team member will be asked to stop assisting with the research processes, and seek medical and psychological input through his/her trusted general practitioner, counsellor, psychologist or psychiatrist.

13.13 Reputational Harm

There are no increased risks of harm to reputation anticipated from this study.

Appendix

Table 1. DSM-IV Symptoms of Major Depressive Disorder and Endicott Substitute Symptoms (Endicott Criteria) [55, 56]

DSM-IV Symptoms	Endicott Substitute Symptoms	Present: Yes/No
Depressed mood most of the day*		
Marked diminished interest or pleasure in all, or almost all, activities most of the day (Anhedonia)*		
~~Weight loss or gain (>5% body weight in a month) / change in appetite~~	Depressed appearance	
~~Insomnia or hypersomnia~~	Social withdrawal or decreased talkativeness	
Psychomotor agitation or retardation		
~~Fatigue or loss of energy~~	Brooding, self-pity or pessimism	
Feeling of worthlessness or excessive or inappropriate guilt		
~~Diminished ability to think or concentrate, indecisiveness~~	Lack of reactivity; cannot be cheered up	
Recurrent thoughts of death, or suicidal ideation or planning, or a suicide attempt		

*One of these symptoms must be present for a diagnosis of major depressive disorder. Each symptom must also meet severity criteria of "most of the day" or "nearly every day" with the duration of greater than 2 weeks. The symptoms must cause clinically significant distress or impairment and are not due to a physiological effect of medication or general medical condition. They must not be better accounted for by bereavement.

The Patient Health Questionnaire-2 (PHQ-2)

Patient Name _____ Date of Visit _____

Over the past 2 weeks, how often have you been bothered by any of the following problems?	Not At all	Several Days	More Than Half the Days	Nearly Every Day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3

Diagram 1. Patient Health Questionnaire-2 (PHQ-2)

Name:_____ Date:_____

Montgomery-Asberg Depression Scale (MADRS)

Instructions: The ratings should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5). It is important to remember that it is only rare occasions that a depressed patient is encountered who cannot be rated on the items in the scale. If definite answers cannot be elicited from the patients, all relevant clues as well as information from other sources should be used as a basis for the rating in line with customary clinical practice. This scale may be used for any time interval between ratings, be it weekly or otherwise, but this must be recorded.

1. ***Apparent Sadness***
Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate on depth and inability to brighten up.
0 No sadness
1
2 Looks dispirited but does brighten up without difficulty.
3
4 Appears sad and unhappy most of the time.
5
6 Looks miserable all the time. Extremely despondent.

2. ***Reported Sadness***
Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or feeling of being beyond help without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.
0 Occasional sadness in keeping with the circumstances.
1
2 Sad or low but brightens up without difficulty.
3
4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
5
6 Continuous or unvarying sadness, misery or despondency.

3. ***Inner Tension***
Representing feelings of ill-defined discomfort, edginess, inner turmoil mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.
0 Placid. Only reflecting inner tension.
1
2 Occasional feelings of edginess and ill-defined discomfort.
3
4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
5
6 Unrelenting dread or anguish. Overwhelming panic.

4. ***Reduced Sleep***
Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.
0 Sleeps as usual.
1
2 Slight difficulty dropping off to sleep or slightly reduced light or fitful sleep.
3
4 Sleep reduced or broken by at least two hours.
5
6 Less than two or three hours sleep.

5. ***Reduced Appetite***
Representing the feeling of loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.
0 Normal or increased appetite.
1
2 Slightly reduced appetite.
3
4 No appetite. Food is tasteless.
5
6 Needs persuasion to eat.

6. ***Concentration Difficulties***
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.
0 No difficulties in concentrating.
1
2 Occasional difficulties in collecting one's thoughts.
3
4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
5
6 Unable to read or converse without great initiative.

7. ***Lassitude***
Representing a difficulty getting started or slowness initiating and performing everyday activities.
0 Hardly no difficulty in getting started. No sluggishness.
1
2 Difficulties in starting activities.
3
4 Difficulties in starting simple routine activities which are carried out with effort.
5
6 Complete lassitude. Unable to do anything without help.

8. ***Inability to Feel***
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.
0 Normal interest in the surroundings and in other people.
1
2 Reduced ability to enjoy usual interest.
3
4 Loss of interest in surroundings. Loss of feelings for friends and acquaintances.
5
6 The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. ***Pessimistic Thoughts***
Representing thoughts of guilt. Inferiority, self-reproach, sinfulness, remorse and ruin.
0 No pessimistic thoughts.
1
2 Fluctuating ideas of failure, self-reproach or self-depreciation.
3
4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
5
6 Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable.

10. ***Suicidal Thoughts***
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and the preparations for suicide. Suicidal attempts should not in themselves influence the rating.
0 Enjoys life or takes it as it comes.
1
2 Weary of life. Only fleeting suicidal thoughts.
3
4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5
6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

Total Score:_____

Diagram 2: Montgomery-Asberg Depression Scale (MADRS)

BRIEF PSYCHIATRIC RATING SCALE (BPRS)

Patient Name _____ **Today's Date** _____

Please enter the score for the term that best describes the patient's condition.

0 = Not assessed, 1 = Not present, 2 = Very mild, 3 = Mild, 4 = Moderate, 5 = Moderately severe, 6 = Severe, 7 = Extremely severe

Score		
☐	1.	**SOMATIC CONCERN** Preoccupation with physical health, fear of physical illness, hypochondriasis.
☐	2.	**ANXIETY** Worry, fear, over-concern for present or future, uneasiness.
☐	3.	**EMOTIONAL WITHDRAWAL** Lack of spontaneous interaction, isolation deficiency in relating to others.
☐	4.	**CONCEPTUAL DISORGANIZATION** Thought processes confused, disconnected, disorganized, disrupted.
☐	5.	**GUILT FEELINGS** Self-blame, shame, remorse for past behavior.
☐	6.	**TENSION** Physical and motor manifestations of nervousness, over-activation.
☐	7.	**MANNERISMS AND POSTURING** Peculiar, bizarre, unnatural motor behavior (not including tic).
☐	8.	**GRANDIOSITY** Exaggerated self-opinion, arrogance, conviction of unusual power or abilities.
☐	9.	**DEPRESSIVE MOOD** Sorrow, sadness, despondency, pessimism.
☐	10.	**HOSTILITY** Animosity, contempt, belligerence, disdain for others.
☐	11.	**SUSPICIOUSNESS** Mistrust, belief others harbor malicious or discriminatory intent.
☐	12.	**HALLUCINATORY BEHAVIOR** Perceptions without normal external stimulus correspondence.
☐	13.	**MOTOR RETARDATION** Slowed, weakened movements or speech, reduced body tone.
☐	14.	**UNCOOPERATIVENESS** Resistance, guardedness, rejection of authority.
☐	15.	**UNUSUAL THOUGHT CONTENT** Unusual, odd, strange, bizarre thought content.
☐	16.	**BLUNTED AFFECT** Reduced emotional tone, reduction in formal intensity of feelings, flatness.
☐	17.	**EXCITEMENT** Heightened emotional tone, agitation, increased reactivity.
☐	18.	**DISORIENTATION** Confusion or lack of proper association for person, place or time.

Diagram 3. Brief Psychiatric Rating Scale (BPRS)

The Clinician Administered Dissociative States Scale (CADSS)
J. Douglas Bremner, Carolyn Mazure, Frank W. Putnam

Name_____ ID_____ Date_____
Subjective Items:

1. Do things seem to be moving in slow motion?
   - 0= Not at all.
   - 1= Mild, things seem slightly slowed down, but not very noticeable.
   - 2= Moderate, things are moving about twice as slow as normally.
   - 3= Severe, things are moving so slowly that they are barely moving.
   - 4= Extreme, things are moving so slowly, I have the perception that everything has come to a stop, as if time is standing still.
2. Do things seem to be unreal to you, as if you are in a dream?
   - 0= Not at all.
   - 1= Mild, things seem a little unreal, but I'm well aware of where I'm at.
   - 2= Moderate, things seem dreamlike, although I know I am awake.
   - 3= Severe, things seem very dreamlike, although I know that I am here, I have the feeling like I might be asleep.
   - 4= Extreme, I feel like nothing is real, like I should pinch myself to wake up, or ask someone if this is a dream.
3. Do you have some experience that separates you from what is happening; for instance, do you feel as if you are in a movie or a play, or as if you are a robot?
   - 0= Not at all.
   - 1= Mild, I feel a little bit separated from what is happening, but I am basically here.
   - 2= Moderate, I feel somewhat separated from what is going on, or I feel as if I am in a movie or a play.
   - 3= Severe, I feel extremely separated from what is happening, but I can understand what people are saying.
   - 4= Extreme, I feel as if everyone around me is talking a foreign language, so that I cannot understand what they are saying, or I feel as if I am on the outside looking in, or like I am a robot or a machine.
4. Do you feel as if you are looking at things from outside of your body?
   - 0= Not at all.
   - 1= Mild, I feel somewhat disconnected from myself, but I am basically all together.
   - 2= Moderate, I feel like I am just outside of my body, but not looking down upon myself from far above.
   - 3= Severe, I feel like I am twenty feet or more away from my body, looking down from above.
   - 4= Extreme, I feel as if I am hundreds of feet above myself, looking down at myself and everyone else here.
5. Do you feel as if you are watching the situation as an observer or a spectator?
   - 0= Not at all.
   - 1= Mild, I feel slightly detached from what is going on, but I am basically here.
   - 2= Moderate, I feel somewhat removed as an observer or a spectator, but I am definitely in this room.
   - 3= Severe, I feel very much as if I am an observer or a spectator, but I am still here in

this room.

4= Extreme, I feel completely removed from what is happening, as if I am not a part of this experience in any way, but totally removed from what is happening, as an observer or a spectator.

6. Do you feel disconnected from your own body?
   - 0= Not at all.
   - 1= Mild, I feel a little bit disconnected from myself, but I am basically all here.
   - 2= Moderate, I feel somewhat detached from my own body, but I am basically all together.
   - 3= Severe, I feel detached from my own body, but not far removed from my body, and I feel as if it is me there.
   - 4= Extreme, I feel like I am completely out of my body, as if I am looking at my own body from a long way off, as if there is another person there.
7. Does your sense of your own body feel changed: for instance, does your own body feel unusually large or unusually small?
   - 0= Not at all.
   - 1= Mild, I have a vague feeling that something about my body has changed, but I can't say exactly what it is.
   - 2= Moderate, I feel like my body has increased or decreased in size slightly, or that it feels somewhat as if it is not my body.
   - 3= Severe, I feel as if my body has increased to twice its normal size, or decreased to twice its normal size, or I very much feel as if this is not my body.
   - 4= Extreme, I feel as if my body has swelled up to at least ten times its normal size, or as if it is ten times as small, or as if my arms have become like toothpicks.
8. Do people seem motionless, dead, or mechanical?
   - 0= Not at all.
   - 1= Mild, people seem a little bit more motionless, dead, or mechanical than would be normal.
   - 2= Moderate, people seem to be at least twice as motionless or mechanical than would be normal.
   - 3= Severe, people seem to be barely moving, or barely alive, or very mechanical.
   - 4= Extreme, it's as if everyone were frozen or completely like machines.
9. Do objects look different than you would expect?
   - 0= Not at all.
   - 1= Mild, things seem slightly different than normal, although it is barely perceptible.
   - 2= Moderate, things are somewhat distorted, but I have no problems recognizing things around me.
   - 3= Severe, things are much more distorted or unreal than normal, but I am able to recognize things in the room.
   - 4= Extreme, like everything is distorted, not real, I feel like I cannot recognize anything, everything is alien or strange.
10. Do colors seem to be diminished in intensity?
    - 0= Not at all.
    - 1= Mild, things seem slightly paler than usual if I think about it.
    - 2= Moderate, colors are somewhat diminished, but still recognizable.
    - 3= Severe, colors are extremely pale, in no way as vivid as they usually are.

4= Extreme, as if everything is in black and white, or all the colors have been washed out.

11. Do you see things as if you were in a tunnel, or looking through a wide angle photographic lens?
    0= Not at all.
    1= Mild, I feel a little bit like I am looking through a tunnel, or a wide angle lens.
    2= Moderate, the periphery of my vision is blacked out, but I still have most of my visual field, or things are somewhat like a wide angle lens.
    3= Severe, it seems as if I'm looking through a tunnel, or through a wide angle lens, but I can see everything clearly.
    4= Extreme, as if I'm looking through a pair of binoculars backwards, where everything around the periphery is blacked out, and I can see a little point of light at the end of a tunnel, with little tiny people and objects, or I am seeing things as if through a wide lens and things are incredibly expanded.
12. Does this interview [assessment, questionnaire] seem to be taking much longer than you would have expected?
    0= Not at all.
    1= Mild, it seems as if this interview has gone on for at least twice as long as the true elapsed time.
    2= Moderate, it seems as if this interview has gone on for at least two hours.
    3= Severe, it seems as if at least ten hours have gone on since the start of the interview.
    4= Extreme, it seems as if time is standing still, so that we have been here at this point in time forever.
13. Do things seem to be happening very quickly, as if there is a lifetime in a moment?
    0= Not at all.
    1= Mild, things are happening slightly faster than normal.
    2= Moderate, things seem to be happening at least twice as fast as normal.
    3= Severe, things seem to be happening at least 10 times faster than normal.
    4= Extreme, as if this whole experience has happened at once, or as if there is a lifetime in a moment.
14. Have there been things which have happened during this interview [assessment] that now you can't account for?
    0= Not at all.
    1= Mild, there may have been things which happened which now I can't account for, but nothing pronounced.
    2= Moderate, at least once there were things which happened which now I can't account for.
    3= Severe, at least twice I have lost several minutes of time, so that now there are things I cannot account for.
    4= Extreme, large pieces of time are missing, of ten minutes or more, so that I am confused about what has happened.
15. Have you spaced out, or in some other way lost track of what was going on during this experience?
    0= Not at all.
    1= Mild, I have had some episodes of losing track of what is going on, but I have

followed everything for the most part.
2= Moderate, I have lost at least a minute of time, or have completely lost track of what is going on now.
3= Severe, I have lost several segments of time of one minute or more.
4= Extreme, I have lost large segments of time of at least 15 minutes or more.

16. Have sounds almost disappeared or become much stronger than you would have expected?
0= Not at all.
1= Mild, things are either a little quieter than normal, or a little louder than normal, but it is not very noticeable.
2= Moderate, things have become about twice as soft as normal, or twice as loud as normal.
3= Severe, things have become very quiet, as if everyone is whispering, or things have become very loud (although not deafening).
4= Extreme, things have become completely silent, or sounds are so loud that it is deafening, and I feel as if I am going to break my eardrums.

17. Do things seem very real, as if there is a special sense of clarity?
0= Not at all.
1= Mild, things seem to be a little bit more real than normal.
2= Moderate, things seem to be more real than normal.
3= Severe, things seem to be very real or have a special sense of clarity.
4= Extreme, things seem to have an incredible sense of realness or clarity.

18. Does it seem as if you are looking at the world through a fog, so that people and objects appear far away or unclear?
0= Not at all.
1= Mild, things seem somewhat foggy and unclear, or I do have the feeling that things are far away, but there is not a major effect on how I perceive things around me.
2= Moderate, things seem very foggy and unclear, or things seem like they are far away, but I can identify the interviewer and objects in the room easily.
3= Severe, I can barely see things around me, such as the interviewer and the objects in the room.
4= Extreme, I cannot make anything out around me.

19. Do colors seem much brighter than you would have expected?
0= Not at all.
1= Mild, colors seem a little bit brighter than normal, but not more than twice as bright.
2= Moderate, colors seem brighter, about twice as bright as normal.
3= Severe, colors seem very bright, at least five times as bright as normal.
4= Extreme, colors seem extremely bright, almost fluorescent, at least 10 times as bright as normal.

20. Do you feel confused about who you really are?
0= Not at all.
1= Mild, I feel a little bit confused about who I am.
2= Moderate, I feel confused about who I am, but I basically know who I am.
3= Severe, I feel very confused about who I am, and at times I wonder if I am a

person, or if I am many people.
4= Extreme, I feel as if there were two or more sides to myself.

21. Do you feel like there are different parts of yourself which do not fit together?
0= Not at all.
1= Mild, I feel like there are different sides of myself, but they're basically part of myself.
2= Moderate, I feel like I have different parts which don't quite fit together.
3= Severe, there are two or more sides to myself which have unique characteristics.
4= Extreme, I have two or more parts to myself with unique personality characteristics.

22. Do you have gaps in your memory?
0= Not at all.
1= Mild, there are some recent things which I cannot remember.
2= Moderate, there have been a few gaps in my memory which lasted a few minutes.
3= Severe, there have been large gaps in my memory which lasted for more than a few minutes.
4= Extreme, I cannot piece together what is happening from one moment to the next due to large gaps in my memory.

23. Do you feel like you have more than one identity?
0= Not at all.
1= Mild, I feel like there is more to me than my personality, but it's basically part of my identity.
2= Moderate, I feel like I have more than one personality, but the personalities are not really distinct.
3= Severe, I have two or more personalities, although they are not fully developed as distinct entities.
4= Extreme, I have two or more personalities which are distinct and have their own names and other unique characteristics.

Diagram 4: The Clinician Administered Dissociative States Scale (CADSS)

Questions for patient *"Have you experienced any of the following symptoms today?* *If yes, how severe were they? "*	**Severity Key** **0 = Never** **1 = Mild** - transient and easily tolerated **2 = Moderate** - caused discomfort and/or interference **3 = Severe** - caused significant discomfort and/or considerable interference	**Participant ID** **Week/Day No:** **Research Nurse/Medical Delegate Name:** **Signature:** **Date:**

Symptoms **Circle relevant items and severity.** Further details can be documented by the clinician in **Clinician Notes** (e.g., any other observations during treatment)	**Baseline** *Time completed :* _____				**Post dose (2 hours)** (Ask patient to rate peak severity) *Time completed :* _____				**Post dose (4 hours)** (Ask patient to rate peak severity) *Time completed :* _____				**Post dose (6 hours)** (Ask patient to rate peak severity) *Time completed :* _____				**Resolved at 6 hours?** *Time completed :* _____		**Clinician Notes**
Dissociation (e.g., felt disconnected from self, body, thoughts, surroundings; feeling strange and/or "spaced out")	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Hallucinations (e.g., seeing, hearing, smelling or tasting things that were not present in reality)	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Problems with memory and/or concentration	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Anxiety	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Restlessness and/or agitation	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Elevated/irritable mood (e.g., euphoria, recklessness, increased energy, increased confidence)	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Tearfulness	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Drowsiness, fatigue, and/or weakness	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	

Dizziness, lightheadedness, feeling faint and/or vertigo (e.g., felt like swaying or spinning)	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Headache	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Numbness and/or tingling of body parts	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Abnormal movements (e.g., tremor, incoordination and/or spasms)	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Vision changes (e.g., blurred vision)	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Hearing changes (e.g., hearing impairment or tinnitus)	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Dry mouth, increased salivation or metallic/unusual taste	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Cardiovascular (e.g., shortness of breath, chest pain and/or palpitations)	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Nausea and/or vomiting	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Skin changes (e.g., rash, itch, yellow discolouration)	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Felt unusually hot, sweaty or cold	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Other – specify: _____	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	Yes	No	
Total =																			

Diagram 5. Modified Ketamine Side Effect Tool (KSET)

The Numeric Pain Rating Scale Instructions

General Information:

- The patient is asked to make three pain ratings, corresponding to current, best and worst pain experienced over the past 24 hours.
- The average of the 3 ratings was used to represent the patient's level of pain over the previous 24 hours.

Patient Instructions (adopted from (McCaffery, Beebe et al. 1989):

"Please indicate the intensity of current, best, and worst pain levels over the past 24 hours on a scale of 0 (no pain) to 10 (worst pain imaginable)"

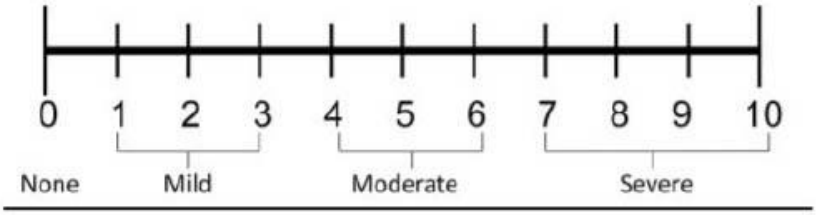


Diagram 6. Numeric Pain Rating Scale (NPRS)

AKPS ASSESSMENT CRITERIA	SCORE
Normal; no complaints; no evidence of disease	100
Able to carry on normal activity; minor sign of symptoms of disease	90
Normal activity with effort; some signs or symptoms of disease	80
Cares for self; unable to carry on normal activity or to do active work	70
Able to care for most needs; but requires occasional assistance	60
Considerable assistance and frequent medical care required	50
In bed more than 50% of the time	40
Almost completely bedfast	30
Totally bedfast and requiring extensive nursing care by professionals and/or family	20
Comatose or barely rousable	10
Dead	0

Diagram 7. The Australia-modified Karnosfky Performance Scale (AKPS)

Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)

Taking everything into consideration, during the past week how satisfied have you been with your.....

	Very Poor	Poor	Fair	Good	Very Good
.....physical health?	1	2	3	4	5
.....mood?	1	2	3	4	5
.....work?	1	2	3	4	5
.....household activities?	1	2	3	4	5
.....social relationships?	1	2	3	4	5
.....family relationships?	1	2	3	4	5
.....leisure time activities?	1	2	3	4	5
.....ability to function in daily life?	1	2	3	4	5
.....sexual drive, interest and/or performance?*	1	2	3	4	5
.....economic status?	1	2	3	4	5
.....living/housing situation?*	1	2	3	4	5
.....ability to get around physically without feeling dizzy or unsteady or falling?*	1	2	3	4	5
.....your vision in terms of ability to do work or hobbies?*	1	2	3	4	5
.....overall sense of well being?	1	2	3	4	5
.....medication? (If not taking any, check here _____ and leave item blank.)	1	2	3	4	5
.....How would you rate your overall life satisfaction and contentment during the past week?	1	2	3	4	5

*If satisfaction is very poor, poor or fair on these items, please UNDERLINE the factor(s) associated with a lack of satisfaction.

Diagram 8. Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)

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