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Pharmacovigilance in hospice/palliative care: Net effect of amitriptyline or nortriptyline on neuropathic pain: UTS/IMPACCT Rapid programme international consecutive cohort

Akram Hussein[1], Madeline Digges[2], Sungwon Chang[3], Jane Hunt[3], Matt Doogue[4,5], Debra Rowett[6], Meera Agar[3], Aynharan Sinnarajah[7], Danielle Kain[8], Simon Allan[9], Jason W Boland[10] and David C Currow[11]

Abstract

Background: Real-world effectiveness of interventions in palliative care need to be systematically quantified to inform patient/clinical decisions. Neuropathic pain is prevalent and difficult to palliate. Tricyclic antidepressants have an established role for some neuropathic pain aetiologies, but this is less clear in palliative care.

Aim: To describe the real-world use and outcomes from amitriptyline *or* nortriptyline for neuropathic pain in palliative care.

Design: An international, prospective, consecutive cohort post-marketing/phase IV/pharmacovigilance/quality improvement study of palliative care patients with neuropathic pain where the treating clinician had already made the decision to use a tricyclic antidepressant. Data were entered at set times: baseline, and days 7 and 14. Likert scales graded benefits and harms.

Setting/participants: Twenty-one sites (inpatient, outpatient, community) participated in six countries between June 2016 and March 2019. Patients had clinician-diagnosed neuropathic pain.

Results: One hundred and fifty patients were prescribed amitriptyline (110) *or* nortriptyline (40) of whom: 85% had cancer; mean age 73.2 years (SD 12.3); mean 0–4 scores for neuropathic pain at baseline were 1.8 (SD 1.0). By day 14, doses of amitriptyline were 57 mg (SD 21) and nortriptyline (48 mg (SD 21). Fifty-two (34.7%) patients had pain improvement by day 14 (amitriptyline (45/110 (43.3%); nortriptyline (7/40 (18.9%)). Thirty-nine (27.7%) had new harms; (amitriptyline 29/104 (27.9%); nortriptyline 10/37 (27.0%); dizziness (n = 23), dry mouth (n = 20), constipation (n = 14), urinary retention (n = 10)). Benefits without harms occurred (amitriptyline (26/104 (25.0%); nortriptyline (4/37 (10.8%)).

Conclusions: Benefits favoured amitriptyline while harms were similar for both medications.

Keywords

Cohort study, amitriptyline, nortriptyline, pharmacovigilance, post-marketing surveillance, neuropathic pain

[1]Hunter New England Health, Newcastle, NSW, Australia
[2]Royal Melbourne Hospital, Parkville, VIC, Australia
[3]IMPACCT, Faculty of Health, University of Technology Sydney, Ultimo, NSW, Australia
[4]Department of Medicine, University of Otago, Christchurch, New Zealand
[5]Department of Clinical Pharmacology, Canterbury District Health Board, Christchurch, New Zealand
[6]Clinical & Health Sciences, University of South Australia, Adelaide, South Australia
[7]Family Medicine and Community Health Sciences, University of Calgary, Calgary, AB, Canada
[8]Department of Medicine, Queen's University, Kingston, ON, Canada
[9]Arohanui Hospice, Palmerston North, New Zealand
[10]Hull York Medical School, University of Hull, Hull, UK
[11]Faculty of Science, Medicine and Health, University of Wollongong, Wollongong, NSW, Australia

Corresponding author:
David C Currow, Faculty of Science, Medicine and Health, University of Wollongong, Northfields Avenue, Wollongong, NSW 2500, Australia.
Email: dcurrow@uow.edu.au

What is already known about this topic?

1. Neuropathic pain is often very difficult to palliate
2. The evidence in palliative care is largely derived from studies in trigeminal neuralgia, post-herpetic neuralgia and painful peripheral neuropathies.
3. It may not be possible to extrapolate from these populations to people with advanced life-limiting illnesses, especially given that many palliative care patients have neuropathic pain from nerve compression.

What this paper adds

1. This real-world data collection demonstrates that amitriptyline appears to be more effective than nortriptyline in the short term reduction of neuropathic pain in people with advanced, life-limiting illnesses.
2. The rates of harms (most of which were mild-moderate) were high at baseline and worsened by the same proportion for each medication.
3. Clinical practice with titration schedules and doses achieved by 14 days show very wide variation.

Implications for practice, theory or policy

1. A minority of patients will have a symptomatic net benefit from the introduction of one of these tricyclic medications within 2 weeks of the medication commencing.
2. A double-blind, head-to-head comparison of amitriptyline or nortriptyline with neuropathic pain is warranted in people with neuropathic pain and an advanced, life-limiting illness.

Background

Neuropathic pain is a prevalent problem affecting more than one in three people in hospice and palliative care settings.[1] It is defined as 'pain initiated or caused by a primary lesion or dysfunction in the nervous system' by the International Association for the Study of Pain (IASP).[2] The management of neuropathic pain remains a challenge for many clinicians as a symptomatic (patient-defined) response to standard non-opioid and opioid analgesics is often inadequate.[3]

Amitriptyline and nortriptyline belong to the class of tricyclic antidepressants. The majority of international guidelines have tricyclic antidepressants among their first line treatment for neuropathic pain, and these drugs are the most commonly used tricyclic antidepressants in those guidelines.[4] The World Health Organisation (WHO) analgesic ladder classifies tricyclic antidepressants as adjuvants that can be added at any stage in the ladder for pain management.[5] Tricyclic antidepressants and other classes of medications such as anti-epileptics drugs are widely used as single agent, first line treatment for neuropathic pain.[6]

Prescribing practice in hospice/palliative care has often been extrapolated from related areas of clinical practice. Despite decades of successful treatment in many people with neuropathic pain due to trigeminal neuralgia, post-herpetic neuralgia or painful diabetic neuropathy, there are no high quality studies in supportive care that demonstrate a net benefit of tricyclic antidepressants in people with a life-limiting illness and neuropathic pain.[7] The most recent evidence suggests amitriptyline probably provides pain relief in about one in four people with neuropathic pain while about one in four of people in this setting report at least one harm.[7] There is much less evidence on the role of nortriptyline for most causes of neuropathic pain.[8] Notably, these studies rarely include people late in the course of a life-limiting illness, a cohort that arguably may differ significantly from other populations with neuropathic pain.

Owing to limited available evidence of treatment effects in palliative care, an international initiative was started in 2011 to improve clinicians' understanding of the net clinical effects of key interventions used in hospice/palliative care.[9] This use of post-marketing (also known as pharmacovigilance/phase IV/quality improvement studies) is one of the initiatives to expand the evidence base for clinical care undertaken by the Australian national Palliative Care Clinical Studies Collaborative (PaCCSC). Such studies can help to understand net effects (benefits and harms) and variations in clinical practice including, in this study, issues such different approaches to dose titration and the dose achieved after titration by 2 weeks.

This study aims to describe the net clinical effects (benefits and harms) of amitriptyline *or* nortriptyline when prescribed for neuropathic pain in a consecutive, prospective cohort of hospice/palliative care patients with life-limiting illnesses, in whom the medication was started as part of routine clinical care. The study also sought to define any baseline clinico-demographic factors that predict benefit or, separately, harms.

Methods

Data collection and the time points at which this happened was defined by an international committee using existing literature of the effects of tricyclic antidepressants for

neuropathic pain. The only data collected were data that would normally be recorded as part of the clinical encounter and no additional data, imaging nor pathology tests were required.

Given that this is a quality improvement initiative to systematically and prospectively collect standardised data at pre-agreed time points on a consecutive case series of patients *once the clinical decision has been made to initiate a tricyclic antidepressant for neuropathic pain*, all participating sites received a waiver from the Human Research Committee or, depending on the jurisdiction, ethical approval for the study as clinical audit/quality assurance programme or low and negligible risk research, respectively.[9,10] The overall programme has ethical approval and receives ethical oversight from the Hunter New England Local Health District Human Research Ethics Committee (approval number 11/04/20/5.13).

Twenty-one sites with inpatient, outpatient and community services participated across six countries (Australia, New Zealand, Canada, England, Hungary and Malaysia) between June 2016 and March 2019. Data were collected for consecutive patients started on either amitriptyline or nortriptyline for neuropathic pain (diagnosed by clinicians in line with their local practice) as part of routine clinical care. Likert scales from the National Cancer Institute's Common Toxicity Criteria for Adverse Events (NCI CTC AE v4) were used to grade benefits and harms.[11] Non-re-identifiable demographic and clinical data were entered onto a secure website (www.caresearch.com.au), customised for this study. No identifiers were made available to the central data repository. For example, age in years and months was collected but not date of birth.

Data were collected at three pre-determined time points prospectively to minimise recall bias after either amitriptyline or nortriptyline was initiated for neuropathic pain: baseline (day 0), at day 7 and at day 14. At each time point, the grade for neuropathic pain was recorded. The severity of neuropathic pain was assessed using the Likert scale from the NCI CTCAE (0, no pain; 1, mild pain; 2, moderate pain limiting instrumental activities of daily living; 3, severe pain with limiting self-care activities of daily living).[10] Overall benefit was defined as a one-point reduction over baseline in this scale at day 14.

Symptoms that may reflect expected harms (defined by an international consensus committee) were recorded at the same points as well as at any time that they arose. Harm was defined as a one-point increase over baseline in the NCI CTCAE criteria for the relevant symptom in the 14-day period. When harms were rated as three or greater on the NCI CTCAE criteria, additional data were entered using a modified Naranjo Adverse Reaction Probability Scale.[12] This questionnaire helps to determine whether reported harms should be attributed to the drug or not. If harms occurred, clinicians were asked to record their clinical responses: (1) no change in medication; (2) medication ceased; (3) dose reduced; or (4) dose increased. Other information recorded included baseline functional status using the Australia-modified Karnofsky Performance Scale and comorbidities using the unweighted Charlson Comorbidity Index.[13,14]

An arbitrary cohort of 100 participants was sought for at least one of the medications being studied. Outcomes are described. No data were imputed. The study is reported using the Strengthening the Reporting of Observational Studies in Epidemiology (collaboration) STROBE guidelines.[15]

Results

Participating sites were drawn from hospice/palliative consultative services, ambulatory clinics and specialist inpatient care units, reflecting the scope of current specialist palliative care practice in the six participating countries.

The clinical and demographic data of the 150 study patients included that 85% of patients had cancer with a mean age of 73.2 years (standard deviation (SD) 12.3; median 74; range 39–97). The mean NCI CTCAE score for neuropathic pain at baseline was 1.8 (SD 1.0; Table 1). Of the 150 patients, 110 were commenced on amitriptyline and 40 were commenced on nortriptyline. The most common underlying mechanism of neuropathic pain in this study was nerve compression or invasion by tumour (45%). *Baseline sympt*oms that were prospectively assessed as potential harms include high rates of urinary retention (23%), constipation (22%) and dizziness (19%) were high at baseline (Table 2).

Patients who were commenced on amitriptyline received an average dose of 53.2 mg daily (SD 22.1; median, 50 mg; range, 10–125 mg) by day 7 days and an average dose of 56.8 mg daily (SD 21.4; median, 50 mg; range, 10–150 mg) by 14 days. Those on nortriptyline received an average dose of 44.3 mg daily (SD 22.1; median, 50 mg; range, 10–100 mg) by day 7 and an average dose of 48.4 mg daily (SD 21.4; median, 50 mg; range, 10–125 mg) by day 14.

Five (3.3%) patients died before day 7 and were excluded from results. Another four people did not have data available at day 14.

Benefit

Within 7 days of starting amitriptyline or nortriptyline, 43 (28.7%) had improvement in pain scores (Table 3). Fifty-two (34.7%) patients had pain improvement by day 14 of whom 37 (24.7%) had total pain resolution. Of these responders, 45/110 (43.3%) were on amitriptyline (mean dose 57.5, SD 22.5, median 50, range 10–150) and 7 (13.5%) were on nortriptyline (7/40 (18.9%); mean dose

Table 1. Baseline clinical and demographic data reflecting hospice/palliative care patients whose data were collected prospectively at the time that amitriptyline or nortriptyline were commenced for neuropathic pain (6 countries; 21 sites).

		N (%)	Median	Range	Mean	SD
Age		145 (97)	74	39–97	73.2	12.3
Gender (male)		79 (53)				
Australian-modified Karnofsky Performance Status Score[14]		149 (99)	50	10–90	53.2	17.2
Body mass index (mg/m^2)		133 (89)	22	14–45	21.9	6.1
C reactive protein (mg/L)		68 (45)	63.1	1–650	117.2	96.8
Weighted Charlson Comorbidity score[13]		150 (100)	8	0–16	7.9	4.8
Unweighted Charlson Comorbidity score		150 (100)	2	0–8	1.7	1.5
Serum albumin levels (g/dL)		122 (81)	3	1.5–4.5	3.0	0.9
International normalised ratio (INR)		37 (25)	1.5	0–5.5	1.6	0.8
Calculated creatinine clearance		112 (75)	73	6 —130	71.9	33.7
Blood glucose levels (mmol/L)		47 (31)	6.4	4 — 20	7.1	3.2
National Cancer Institute Common Toxicity Grading for neuropathic pain		150 (100)	2	0–4	1.8	1.0
Primary life limiting illness	Advanced cancer	127 (85)	Underlying mechanism of neuropathic pain	Nerve compression or invasion by tumour	68 (45)	
	End stage renal failure	4 (3)		Diabetic neuropathy	17 (11)	
	Hepatic failure	3 (2)		Post-herpetic neuralgia	14 (9)	
	Cardiac failure	2 (1)		Spinal cord injury	12 (8)	
	Respiratory failure	3 (2)		Chemotherapy	16 (11)	
	Other	11 (7)		Other	23 (15)	

Table 2. Baseline symptoms of interest that were prospectively assessed as potential harms when amitriptyline or nortriptyline were introduced for the symptomatic reduction of neuropathic pain in hospice/palliative care patients (*n* = 150).

Baseline symptoms**	*n* (%)	Severity	
		Median	Range
Somnolence	3 (1)	1	1–2
Hallucination	7 (3)	1	1–2
Delirium	1 (1)	1	1–1
Confusion	15 (6)	1	1–3
Urinary retention	56 (23)	1	1–3
Constipation	53 (22)	1	1–3
Supraventricular tachycardia	1 (1)	1	1–1
Dry mouth	14 (6)	1	1–3
Dizziness	46 (19)	2	1–3
Palpitation	10 (4)	1	1–2
Syncope	1 (1)	1	3–3
Other	35 (14)	1	1–3

**Patient could have more than one baseline symptom.

49.3, SD 12.5, median 75, range 10–125). Only two patients had worse pain scores over 14 days and they were both on amitriptyline (25 and 50 mg). Eighty-seven (58.0%) patients had no improvement, of whom 59/104 (56.7%) were on amitriptyline; (mean dose 55.4, SD 24.7, median 50, range 10–150) and 30/37 (81.1%) were on nortriptyline (30/37 (81.1%); mean dose 44.3, SD 13.2, median 50, range 10–125).

Harms

Thirty-nine (27.7%) patients had new harms recorded after baseline; 29/104 (27.9%) for amitriptyline and 10/37 (27.0%) for nortriptyline (Table 3). The most frequently encountered new harms were dizziness (*n* = 23), dry mouth (*n* = 20), constipation (*n* = 14) and urinary retention (*n* = 10). Dizziness, dry mouth and constipation had a median severity of 2. Only six patients had their medication ceased because of harms (2/104 (1.9%) for amitriptyline and 4/37 (10.8%) for nortriptyline), while for four patients the dose was reduced (all on nortriptyline (10.8%). Five experienced a harm of grade 3 or higher which were all assessed using the modified version of the Naranjo scale categorising two harms as 'probable', two as 'possible' and one as 'doubtful'.

The total number of patients who received benefit from either amitriptyline (26/104 (25.0%)) or nortriptyline (4/37 (10.8%)) without a harm was 30/141 (21.3%).

Discussion

This study provides important information on the use and outcomes of amitriptyline or nortriptyline for neuropathic pain in routine clinical care of patients with life-limiting illnesses from six countries using their respective clinical guidelines. We pooled the data for these tricyclic antidepressants as they reflect the prescribing practice in palliative care facilities from different parts of the world for neuropathic pain.

Table 3. Overall net effects (benefits and harms) on day 14 using prospectively collected, standardised data in 150 hospice/palliative care patients who were prescribed amitriptyline or nortriptyline for the symptomatic reduction of neuropathic pain (6 countries; 21 sites).

#Total Neuropathic pain Benefit/s n (%)	Drug	##Harm(s)	Actions by day 14	*N* (%)
Yes *n* = 52/150 35.9%	Amitriptyline *n* = 45/52 86.5%	Yes *n* = 15/45 33.3%	Medication cessation (1) No change in med (15)	1 (1) 15 (14)
		No *n* = 26/45 57.8%	No change in med (21) Medication cessation (2) Dose reduction (2) Dose increased (1)	21 (20) 3 (3) 2 (2) 1 (1)
		NR *n* = 2/45 4.4%		
		Died *n* = 2/45 4.4%		
	Nortriptyline *n* = 7/52 13.5%	Yes *n* = 2/7 28.6%	Medication cessation (1) No change in med (1)	1 (1) 1 (1)
		No *n* = 4/7 57.1%	No change in med (1) Medication cessation (2) Dose increased (1)	1 (1) 2 (2) 1 (1)
		NR *n* = 1/7 14.3%		
No *n* = 89/150 61.4%	Amitriptyline *n* = 59/89 66.3%	Yes *n* = 14/59 23.7%	Medication cessation(3) Dose reduction (3) No change in med (8)	3 (3) 3 (3) 8 (8)
		No *n* = 41/59 69.5%	No change in med (37) Medication cessation (2) Dose increased (4)	37 (36) 2 (2) 4 (4)
		NR *n* = 2/59 3.4%		
		Died *n* = 2/59 3.4%		
	Nortriptyline *n* = 30/89 33.7%	Yes *n* = 8/30 26.7%	No change in med (6) Medication cessation (1) Dose reduction (1)	6 (6) 1 (1) 1 (1)
		No *n* = 20/30 66.7%	No change in med (12) Dose increased (7) NR (1)	12 (11) 7 (2) 1 (1)
		NR *n* = 1/30 3.3%		
		Died *n* = 1/30 3.3%		
Not recorded *n* = 4/150 2.8%	NR *n* = 4	Yes *n* = 1/4 25.0%	No change in med (1)	1 (1)
		NR *n* = 3/4 75.0%		
Died before day 7 *n* = 5/150 3.3%				

Firstly, this study reflects wide variation in titration schedules and the doses of these medication achieved by 2 weeks. Further work needs to be done to understand the decision-making processes that underpin such wide variation. The current study cannot define whether either titration or maximum effective doses were optimised.

Reflecting on real-world practice raises important questions for future research.

A majority of patients in this observational study had advanced metastatic cancer as their life-limiting illness with a number of underlying causes of neuropathic pain identified at baseline. This study provides additional, real-world evidence for the net effectiveness of these tricyclic antidepressants, with up to two in five patients achieving some reduction in pain by 2 weeks using amitriptyline and one in four achieving a reduction in pain without harms. These results largely accord with data available from systematic reviews.[16,17]

In addition to neuropathic pain, there were multiple symptoms reported by patients at baseline. The most frequently reported were dizziness, dry mouth, constipation and urinary retention. Of note, these may all reflect the anti-cholinergic load to which tricyclic antidepressants contribute. Minimising anticholinergic load by reviewing all medications that contribute and ceasing any that are no longer necessary is required when initiating tricyclic antidepressants in people who are frail, especially the elderly, given that anticholinergic load is a frequent cause of delirium.[18,19] One in four patients had additional harms recorded after starting the medication, almost all of which were mild to moderate in severity. One half of the patients that reported harms had dose reduction or medication cessation indicating that these harms were troublesome to patients, and their clinicians responded.

The available evidence on the effectiveness and tolerability of either amitriptyline or nortriptyline for neuropathic pain in adults in the literature is consistent with our findings. A 2017 meta-analysis found that one in four people with neuropathic pain probably had pain relief and about one in four of them having at least one adverse events.[7] In keeping with the findings in this study, a similar meta-analysis in 2017 found very little evidence to support the use of nortriptyline to treat neuropathic pain.[8]

Strengths

Using a multi-centre, multi-national, multi-setting prospective design, this study helps to provide evidence on the real-world clinical performance of amitriptyline or nortriptyline when prescribed for neuropathic pain in people with life-limiting illnesses. At present there is no high-quality evidence to support their current prescribing patterns for hospice/palliative care patients due to a lack of studies and the difficulty of conducting such studies.

This study treated the use of either amitriptyline or nortriptyline as a single approach to reflect the prescribing patterns of tricyclic antidepressants as an established first line for neuropathic pain from international guidelines.

Limitations

This study uses a pragmatic methodology to capture accurately current clinical practice from an unselected consecutive cohort of people with life-limiting illnesses. This approach does not standardise the clinical approach (such as standardising the diagnostic tools) but rather reflects what happens after a clinician has made the therapeutic decision to treat for the neuropathic pain that they have diagnosed. Reasons for dose titration were not captured nor the day on which it occurred but wide variation was seen.

Clinical implications

Given the lack of evidence that evaluates the use of amitriptyline or nortriptyline for neuropathic pain in patients with life-limiting illnesses, this study gives some insights into patients' outcomes with the balance of benefit favouring amitriptyline in this clinical setting. The population, which mainly includes patients with cancer, is consistent with that served by many hospice/palliative care organisations.

Future research directions

A direct head-to-head comparison of amitriptyline and nortriptyline is warranted in neuropathic pain for people with life-limiting illnesses given the very different response profile identified in this study. Further, there is no agreed dose titration schedule for tricyclic antidepressants when used for neuropathic pain in people with life-limiting illnesses. This study has given an overall insight in the tolerability and efficacy of current prescribing practices of amitriptyline or nortriptyline in this setting. We found that the majority of neuropathic pain in this study arose from nerve compression or invasion by tumour. Studying a dose titration on this neuropathic pain will further refine the evidence for clinicians.

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Authorship

All authors have made a substantial contribution to the concept or design of the work; or acquisition, analysis or interpretation of data, drafted the article or revised it critically for important intellectual content and approved the version to be published.

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Data availability

Data are available to bona fide researchers from IMPACCT, University of Technology Sydney, Ultimo, NSW, Australia, 2007.

ORCID iDs

Meera Agar https://orcid.org/0000-0002-6756-6119
Aynharan Sinnarajah https://orcid.org/0000-0002-7967-159X
Jason W Boland https://orcid.org/0000-0001-5272-3057
David C Currow https://orcid.org/0000-0003-1988-1250

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