



Adjunctive Vitamin D in the treatment of non-remitted depression: Lessons from a failed clinical trial



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ABSTRACT

Background: Many patients with depression fail to achieve remission after several consecutive treatments. Vitamin D deficiency is prevalent and new research suggests that it may have an impact on mood, primarily through an effect on neurotransmitters. Numerous observational studies suggest a relationship between low levels of vitamin D and increased incidence and severity of mood disorders. A small number of pilot studies have been undertaken but lack rigorous methodology required to draw conclusions about a clinical role for this nutrient in treatment resistant depression.

Methods: This study was designed as a randomized, double-blind, placebo controlled intervention study administering a weekly (bolus) dose of 28 000IU of Vitamin D3 or placebo to 125 patients with non-remitted depression adjunct to current antidepressant medication. Patients were followed weekly for eight weeks plus a one month follow up. Outcomes measured included depression severity, serum vitamin D levels and safety. Due to slow recruitment during the first season, amendments were made. These included extending the age range to 18–75 and removing the requirement for failing to respond to one pharmacologic antidepressant agent. The protocol was amended to reduce the burden on participants by changing the in-office visits to bi-weekly. Three additional tertiary psychiatric clinics were also added as trial sites.

Results: Over three recruitment period years (fall/winter), a total of 148 participants completed screening, 24 (16.2%) of whom qualified to participate in the study. Use of too many or no psychiatric medications, comorbid exclusionary psychiatric conditions, current use of a vitamin D supplement, and lack of participant compensation were the predominant reasons for ineligibility or unwillingness to participate. 9 participants were successfully enrolled in the study, 7 (77.8%) of whom completed the trial as per the protocol. After the third season, futility was declared based on inability to enroll participants. The sample size of enrolled participants (7/125, 5.6%) lacks power to conduct a full assessment of findings.

Discussion: High accessibility of vitamin D, as well as a growing lack of equipoise in patients and clinicians about the potential ubiquitous benefits of vitamin D for Canadians, not just for mood disorders, resulted in a large proportion of ineligible potential participants. Limited funding provided to studies on natural health products hampered recruitment. The labile and fluctuating nature of non-remitted depression as well as frequent comorbid conditions creates additional challenges for conducting trials in this population. Future studies assessing vitamin D in depression should consider our experiences in design and conduct of research. Innovations in clinical trial design such as preference trials or accepting patients already using vitamin D but not achieving an optimal target value are potential solutions to some of these challenges.

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1. Introduction

Depression and other mood disorders are a major health concern globally with significant impact on quality of life, morbidity, and mortality. While antidepressant medications are beneficial for some patients, many fail to achieve remission after several consecutive treatments.¹ A recent Canadian study found that 22% of a large sample of depressive patients failed to respond to at least two consecutive antidepressant agents.² Despite the increasing prevalence of treatment-resistant depression, significant challenges to psychopharmacology management remains, with recent guidance documents identifying a dearth of evidence and limitations to most strategies for optimal management.^{3, 4}

While most vitamin deficiencies are rare in the developed world, vitamin D deficiency remains prevalent, likely due to low sun exposure at northern latitudes, a trend toward increasing indoor activity and concern about the risks of excess sun exposure.⁵ New research suggests that deficiency of vitamin D may have an impact on mood, primarily through an effect on neurotransmitters.⁶ Vitamin D is a neurosteroid, capable of crossing the blood-brain barrier, with physiological effects on neuroprotection, neuroplasticity, brain development, and regulation of neurotrophic factors.⁷ High concentrations of vitamin D receptors on neurons and glia have been reported in many areas of the brain including the hippocampus and cingulate cortex.⁸ These neurobiological findings provide support for a plausible mechanism of vitamin D as an influencer on mood, as well as a potential factor in prevention and treatment of mood disorders like depression. Still, there remains some dispute regarding the validity of some of the studies on vitamin D.⁹

Numerous observational studies suggest a relationship between low levels of vitamin D and increased incidence and severity of mood disorders.¹⁰ A 2013 systematic review and meta-analysis found a statistically significant inverse relationship between serum vitamin D levels and the risk of depression when analyzing the observational data.¹¹ A number of pilot intervention studies have been undertaken to examine vitamin D's therapeutic potential and several showed promising results. Due to small sample sizes,^{6, 12, 13} inadequate control and blinding,⁶ non-clinically depressed patient populations^{14–18} a diagnosis of seasonal affective disorder,¹⁹ the presence of other comorbidities,²⁰ and use of assessment tools lacking validation²¹ these studies lacked rigorous methodology required to draw conclusions about a clinical role for this nutrient in treatment resistant depression.

A 2014 systematic review and meta-analysis reported no overall effect on depressive symptoms when analyzing all of the studies with depression outcomes.²² However, in subgroup analysis of two of the studies that enrolled patients with clinically significant depression, the effect was shown to be a statistically significant decrease in depression severity. This suggests that the benefit of vitamin D supplementation may be most significant in a clinically depressed population, however, the small number of studies conducted indicate that further research is needed.

Because of the need for adjunctive treatment options, strong epidemiological evidence, proposed mechanisms, and preliminary pilot study data, we sought to complete a randomized, controlled trial using vitamin D as an adjunctive therapy in patients with non-remitted depression to see if improvements in depression would occur.

2. Methods

2.1. Study design

This study was designed as a pilot randomized, double-blind, placebo controlled, parallel intervention study in 125 patients with non-remitted depression. Patients were randomized to either vitamin D supplementation or placebo (allocation ratio 1:1). Enrollment and trial participation took place during the fall and winter months (October to April, inclusive) to minimize natural vitamin D from sun exposure. The

study was registered at ClinicalTrials.Gov (NCT02072187). Funding was provided by a competitive grant obtained from the Lotte and John Hecht Foundation. Ethical approval and oversight was provided by an independent IRB (Optimum) and the REB of the Canadian College of Naturopathic Medicine. Permission to conduct the study was given by Health Canada.

Patients completed a telephone screen followed by a screening visit which included informed consent, the M.I.N.I. International Neuropsychiatric Interview (MINI), assessment of serum vitamin D levels (25(OH)D) and liver and kidney function tests, collection of social history and demographic information, medical, medication and psychiatric history, assessment of vital signs, completion of a physical examination. Subsequently, participants were followed weekly for eight weeks plus a one month post-intervention follow up. Each visit included an assessment of efficacy through the use of validated questionnaires and an assessment of safety.

Randomization was completed centrally through computer generation. Simple randomization (i.e. virtual coin flip) was used to determine group allocation for each participant. The only person aware of the allocation was a pharmacist. The pharmacist labeled the study product with sequential numbers which corresponded to participant number and followed the allocation sequence. A back up copy of the random allocation sequence was kept in the clinic in a sealed envelope. The pharmacist had no contact with study participants.

2.2. Participant selection

Eligible participants were 18–65 years of age who met criteria for major depressive disorder (score of greater than 7 on the Hamilton Depression Scale) after treatment of at least 8 weeks with an adequate dose of a single first line pharmacological antidepressant agent. Exclusion criteria included: any comorbid Axis I disorder (with the exception of comorbid anxiety disorders if MDD was deemed to be the primary diagnosis), cognitive disorders, risk of suicide, formal psychotherapy commenced in the 30 days prior to screening, use of any other psychiatric medications (apart from a short half-life hypnotic used as needed for insomnia), history of parathyroid disease, kidney stones, or other serious medical illness, pregnancy or current breastfeeding, use of natural health products deemed to have antidepressant effects or supplementation of vitamin D at a dose greater than 200IU per day in the past 6 months. Lastly, patients were excluded if baseline serum vitamin D was greater than 150 nmol/L.

Participants were able to withdraw their consent at any time, and were eligible to be withdrawn from the study if, on the basis of the study clinician's subjective assessment, the participant's depression was deemed to have seriously worsened or a risk of suicide became apparent. The clinician was aware of participants' identity and past medical history in order to select a rescue medication and inform an individualized course of treatment if needed. A data safety monitoring board (DSMB) was in place to address adverse events in the study, as well as provide additional advice and oversight of any participant withdrawals.

The study was conducted at the START Clinic, a tertiary psychiatry clinic in Toronto, Ontario, Canada. Participants were recruited from the patient database at the START Clinic, as well as new referrals to the clinic. Letters were mailed to Medical Doctors in the surrounding area with an invitation to refer non-remitted depression patients. Additionally, online classified postings and print advertisements were created. Additional trial sites were located at the Chatham-Kent Health Alliance in Chatham, Ontario, Canada, a small community hospital, and Eden Mental Health Centre in Winkler, Manitoba, Canada, a small psychiatric hospital providing inpatient and outpatient services.

2.3. Intervention

The intervention was a weekly bolus dose of 28 000IU of Vitamin

D3 (cholecalciferol), the equivalent of 4000IU per day, or placebo. The vitamin D formula contained the following non-medicinal ingredients: water, gum arabic, and sesame oil. The placebo formula contained all non-medicinal ingredients but no vitamin D and appeared, smelled, and tasted the same as the active formula. The formula was a liquid and dispensed on a disposable spoon by the study coordinator at each weekly study visit. The participants continued to take their previously prescribed anti-depressant medication for the duration of the study without changing the dose. They were not permitted to begin a new medication or any nutritional supplement with a theoretical effect on depression.

2.4. Outcomes

The primary outcome was effect on depression, measured through patients' responses on the Beck Depression Inventory-II (BDI-II) and the Fawcett-Clark Pleasure Capacity Scale (FCPS). Additionally, the Beck Anxiety Inventory (BAI), Intolerance of Uncertainty Scale (IUS) and Sheehan Disability Scale (SDS) were used to assess other aspects of mental wellbeing and quality of life.

2.5. Instruments

Beck Depression Inventory-II (BDI-II): The BDI-II is a 21-item self-report measure designed to assess the presence and severity of depression. Items are based on DSM-IV diagnostic criteria for MDD and are rated on a 4-point present-state severity scale.²³ Test items describe possible feelings within the past two weeks, and subjects are asked to rate how much these statements parallel their own feelings using a four-point Likert scale (higher scores coinciding with a greater degree of depression). The scores range from 0 to 63, with scores of 0–13 indicating minimal depression, 14–19 mild depression, 20–28 moderate depression, and 29–63 severe depression. The BDI II has demonstrated excellent psychometric properties with good internal consistency ($\alpha = 0.91$)²⁴.

Intolerance of Uncertainty Scale (IUS): The IUS assesses intolerance to uncertainty, and follows a four-factor structure representing the ideas that uncertainty i) is stressful and upsetting, ii) leads to the inability to act, iii) uncertain events are negative and should be avoided, and iv) being uncertain is unfair. This 27 item scale includes items such as “Uncertainty keeps me from living a full life” and “Unforeseen events upset me greatly”. Participants rate each item on a five-point Likert scale ranging from 1 = ‘not at all characteristic of me’, to 5 = ‘entirely characteristic of me’. The IUS has demonstrated good test-retest reliability over 5 weeks, $r = 0.78$ and has an excellent internal consistency, $\alpha = 0.91$.^{25, 26}

Beck Anxiety Inventory (BAI): The BAI is a self-report scale designed to evaluate the severity of physical symptoms of anxiety over the past week.^{27,28} Participants rate the 21 items on a 4-point severity scale from 0 = ‘not at all’ to 3 = ‘severely, I could barely stand it’. Total response scores range from 0 to 63, with higher scores indicating more severe anxiety. The BAI possesses adequate test-retest reliability and convergent validity.²⁹

Fawcett-Clark Pleasure Capacity Scale (FCPS): The FCPS is a 36-item questionnaire assessing a participant's current pleasure capacity on a 5-point Likert scale.³⁰ Participants are asked to rate their hedonic responses to hypothetical situations regarding several areas such as social activity, sensory experiences and sense of mastery of difficult tasks. Higher scores for each item indicate a higher hedonic capacity.³⁰ Although frequently administered to assess anhedonia, the reliability and validity of this measure has not been widely studied.³¹ D'haenen.³² suggests its concurrent validity and reliability is satisfactory, while Leventhal and colleagues demonstrate the FCPS to have a significant factor loading from Hedonic Capacity.³⁰

Sheehan Disability Scale (SDS): The SDS is a measurement of functional disability and impairment due to psychiatric symptoms.³³

The SDS is made up of 5 items that measure the extent a patient is impaired by the disease. It evaluates 3 inter-correlated domains (work/school, social life, and family life/home responsibilities) and measures the number of unproductive or under-productive days. Each of the three domains is rated from 0 to 10 (no impairment to most severe impairment) with evaluation of not at all,⁰ mild,^{1–3} moderate,^{4–6} marked,^{7–9} and extreme.¹⁰ disability. A score of 30 indicates most severe impairment.³³

Additionally, safety was assessed at each visit using non-leading questions such as “Have you felt different in any way since the last visit?”. Serum vitamin D was reassessed at the study mid-point, final visit and follow-up to ensure that levels did not exceed the recommended 150 nmol/L. Vital signs were reassessed at the study mid-point, final visit and follow-up and a physical examination was repeated at the final visit and follow-up.

2.6. Sample size determination

As this is a pilot study, a formal sample size calculation was not possible. Responder (> 50% improvement on symptoms) rates from a treatment resistant depression population vary widely, although one study estimates this to be approximately 12% for patients receiving ‘usual care’.³⁴ We anticipated that the vitamin D group would experience an approximate 10 point reduction on their BDI scores, resulting in approximately 20% achieving ‘responder’ status. Using these effect size estimates, and incorporating a Type 1 Error of 0.05, 80% power will be achieved if 125 people are recruited. This plan allowed for up to a 25% participant withdrawal/dropout rate and still ensured that the study was adequately powered based on the assumptions outlined above.

2.7. Statistical analysis

In order to assess if there was a change in scores over time for both groups while investigating covariates such as baseline serum vitamin D and change in vitamin D levels over time, an ANOVA was to be conducted. The primary outcome measure of interest was the change in total depression measure scores (BDI-II scores) from baseline to the last observed visit. This continuous efficacy variable comparison was analysed using a student's *t*-test for between group differences and χ^2 tests for dichotomous variables (i.e., responder rates). Results generated by the remaining (secondary) outcome measures were analysed using a *t*-test. All parametric tests will be 2-tailed and calculated using a 5% alpha level. Analyses were planned to be conducted on an intention to treat basis using the last observation carried forward from all participants who received at least one administration of study product.

2.8. Protocol amendments

Due to slower than expected enrollment during the first season, several amendments were made in an attempt to increase recruitment and eligibility. Because of interest from older patients, the age range was extended from 18 to 65 to 18–75 years of age. Subsequently, the requirement for failing to respond to one pharmacologic antidepressant agent was removed, thus including patients taking no medication or multiple medications. Three additional tertiary psychiatric clinics were added as trial sites to increase exposure. Finally, the protocol was changed to reduce the burden on participants by changing the in-office visits to bi-weekly and including a weekly phone call to assess for safety and ongoing eligibility. All amendments were approved by Health Canada and the Research Ethics Boards.

3. Results

Over three recruitment period years (October to April, from 2013 to 2016), a total of 148 individuals completed phone screening. At the START Clinic, the primary study site, 40 individuals from the clinic

Table 1
Referral sources for individuals screened for participation, all study sites combined.

Referral Source	Number of Individuals
Referral by a study doctor	40
START Clinic Database	40
Online classified posting	34
Unknown	18
Newspaper Advertisement	16
Posters in local doctors' offices	8
Canadian College of Naturopathic Medicine website	7
Referral by an external doctor	6
Clinical Trials Registry website	4
Word of mouth	3
Radio	3

database who were potentially eligible were contacted and offered an opportunity to complete the phone screen. 3 individuals were referred to the study by doctors – 2 by clinicians involved in the study and 1 by local medical doctors. Patients responded to postings and advertisements about the study on online classified pages ($n = 34$), the Canadian College of Naturopathic Medicine website ($n = 7$), the Clinical Trials Registry website ($n = 4$), in the newspaper ($n = 16$), the radio ($n = 3$) and a poster displayed in local medical doctors' offices ($n = 8$). Three patients heard about the study word of mouth and 18 individuals did not disclose a referral source or could not be contacted. At one additional site the two patients who completed screening were referred by a study clinician and at the second, 23 patients were referred by a doctor involved in the study and five were referred by doctors external to the study. See Table 1 for a complete review of sources of subject recruitment.

A complete visual outline of study protocol pathway and participants is shown in Fig. 1.

Of 179 inquiries and 148 individuals screened, 24 (16.2%) qualified to participate in the study. The reasons for failing to qualify included: medication ($n = 51$, 25 taking no medication, 20 taking multiple medications, 4 recently changing medications, 2 taking a low dose of a medication), lack of interest/time commitment in completing screening questionnaire ($n = 14$), comorbidities ($n = 23$), age greater than 65 years ($n = 5$), current vitamin D supplementation ($n = 17$), not interested without compensation ($n = 6$), didn't meet criteria for current MDD ($n = 3$), not willing to travel to the clinic ($n = 2$), trying to conceive ($n = 1$), no provincial insurance ($n = 1$). An additional 24 individuals who expressed interest could not be reached by phone and 7 individuals contacted the study outside of the recruiting season but could not be re-contacted during recruiting. Table 2 outlines the specifics of why people were deemed ineligible.

Of the 24 individuals who qualified on the phone screen, 9 participants were successfully enrolled in the study. The most common reasons for unwillingness to participate included a lack of interest ($n = 12$), scheduling conflict ($n = 2$) and loss to follow up ($n = 1$). Table 3 outlines the baseline characteristics of the enrollees.

Of the 9 patients who enrolled, seven participants completed the study (77.8% completion rate). One participant was withdrawn after 5 visits at the discretion of the study clinician due to subjective assessment of worsening anxiety and depression symptoms and indication for an increase in the participant's medication dosage. A second patient chose to withdraw after 3 study visits due to interest in participating in another clinical trial; although randomized, they had not received any study medication.

Aside from the participant that was withdrawn due to worsening of the condition being studied, no other adverse events were reported. No changes were observed on physical examination at the midpoint or conclusion of the study. No participants had midpoint or final serum vitamin D levels that exceeded 150 nmol/L, a level which has been deemed to be toxic or associated with significant risk.³⁵

After the third season, futility was declared based on inability to

enroll participants. The sample size of enrolled participants (7/125, 5.6%) lacks power to conduct a full assessment of findings. A preliminary assessment of the available data shows a trend towards improvement in BDI, BAI, FCPCS and SDS scores; however, very high levels of variability among the small number of participants precludes any conclusions. Mean scores, using the last observation carried forward, are presented in Table 4. Additionally, among participants who completed the study, meaningful increases in serum vitamin D levels were observed.

4. Discussion

The question of the role of vitamin D in the development and progression of mood disorders is relevant and warrants thorough investigation. While this study was not able to answer the question of this nutrient's clinical utility, the challenges that it faced highlight some of the difficulties of assessing vitamin D as an intervention in the non-remitted depression population and may serve to guide future clinical trials in this area. Clinical trials with low enrollment deplete resources and increase costs and delay the availability of clinical information.³⁶

There were many factors that may have contributed to the difficulty experienced in recruiting and enrolling patients. Some of the challenges could be related to using vitamin D as an intervention. There is a growing lack of equipoise among patients and clinicians about the potential ubiquitous benefits of vitamin D for Canadians, not just for mood disorders. Numerous guidelines have been produced in recent years.³⁷ including a 2007 recommendation from Health Canada to supplement 400IU of vitamin D in all adults 50 years of age or older. In the same year, the Canadian Cancer Society recommended 1000IU of vitamin D supplementation for all Canadian adults and 2010 recommendations from Osteoporosis Canada included supplementation of 400 to 2000IU of vitamin D for bone health promotion based on risk level.³⁸ Further, a Cochrane review suggested that vitamin D supplementation in an elderly population may decrease all-cause mortality.³⁹

Vitamin D deficiency has received widespread media attention and many consumers are choosing to purchase supplements which are widely available, accessible without a prescription and low in cost. A recent study estimated that in 2007–2009, 31% of Canadians had taken a vitamin D-containing supplement in the prior month.⁴⁰ Because current vitamin D supplementation was an exclusionary criterion in this protocol, many individuals were deemed ineligible. Furthermore, with the growing public perception that vitamin D may be helpful in maintaining mood, particularly in the winter, the draw of a potentially novel treatment may not have been present in this study to outweigh the possibility of being randomized to receive the placebo formula. A recent study assessing participant motivations for participation in a clinical trial found that 91.4% expected to personally benefit from the study.⁴¹ In this case, individuals expecting to benefit from vitamin D had the option of easily purchasing the nutrient rather than participating in a study involving multiple clinic visits, blood draws and the possibility of placebo allocation. Additionally, the prominent motivation of personal gain from participation may have also limited the participation of individuals who did not believe that vitamin D was a potentially useful therapy. One patient who declined participation reported that he was “skeptical of vitamin D” and others sharing similar beliefs may have chosen not to contact the study.

Many challenges arose as a result of the patient population selected for this study. Conducting research in patients with depression is challenged by a heterogeneous population, a lack of biomarkers and high rates of comorbidity.⁴² While the non-remitted depression population allows for ethical use of an unproven therapeutic agent as an adjunctive treatment, there were limitations. Non-remitted depression, like other mood disorders often follows a progression or relapsing and remitting.⁴³ Treatment-resistant depression is known to have a more complex clinical course than treatment-sensitive depression.² Despite reporting ongoing depression, some patients failed to meet the criteria

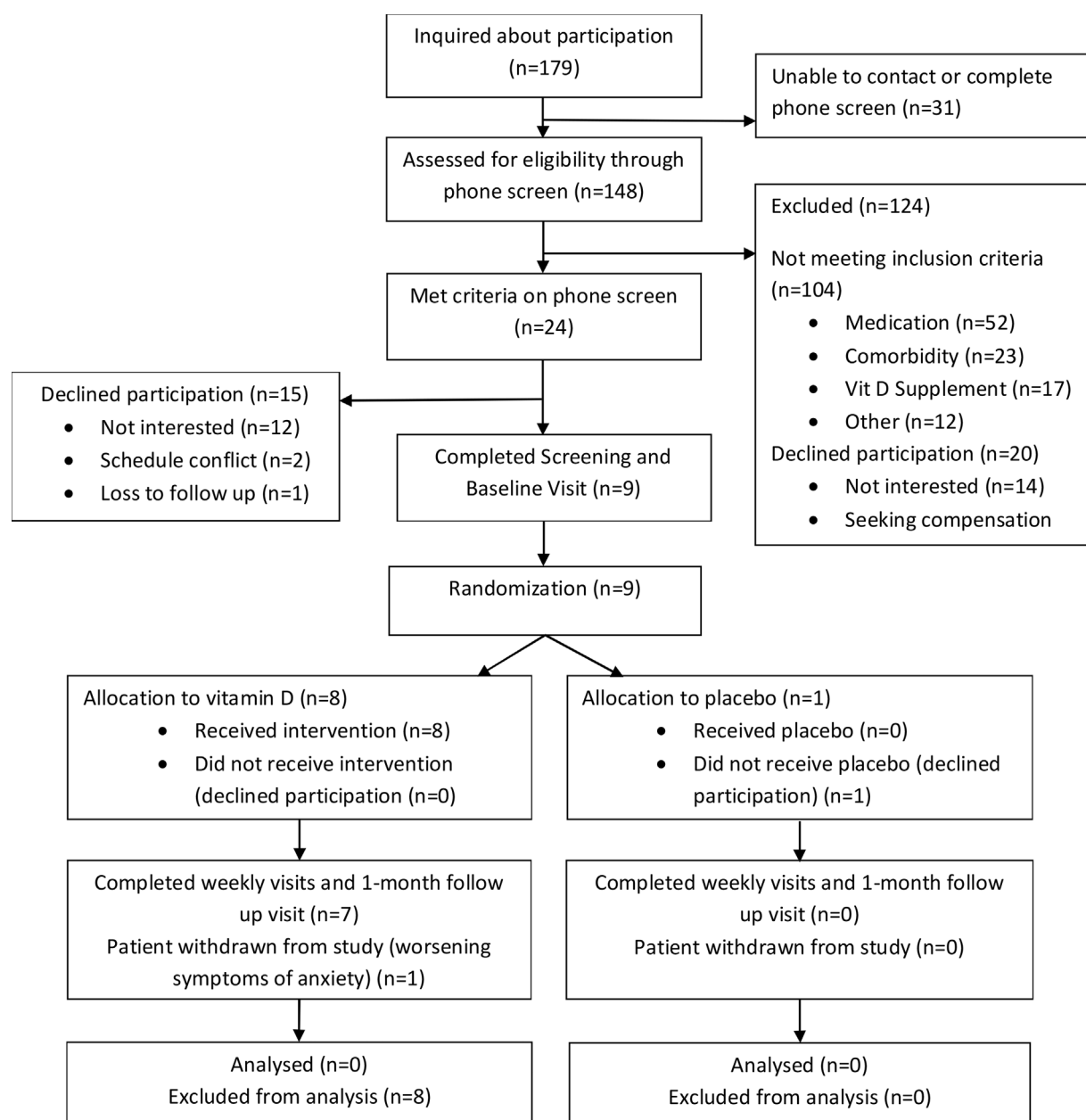


Fig. 1. Enrollment and involvement pathway, CONSORT Flow Diagram.

Table 2
Reasons for failing to qualify for enrollment.

Reason for failing to qualify	Number of Individuals
Medication	51
Comorbid psychiatric condition	23
Current Vitamin D Supplementation	17
Not interested	14
Seeking compensation	6
Age (above limit)	5
No current MDD	3
Travel concerns	2
Trying to conceive	1
No OHIP card	1

for MDD at the time of screening for this study. Conversely, some experienced aggravation in their symptoms around the time of screening and were prescribed additional new therapies or adjustments to their pharmacotherapy protocol which excluded them from participation as

the new medication would have added a degree of difficulty in interpreting results.

Another challenge to recruitment was a high frequency of comorbid conditions in the patients screened for eligibility. In order to assess the role of vitamin D in depression and avoid confounding factors, we sought to exclude other psychiatric conditions; however, the number of individuals who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for another psychiatric diagnosis when completing the MINI was significant. This may have been a result of the patient population of this study. Patients with treatment-resistant depression have higher rates of Axis I, II and III disorders compared to patients with treatment-sensitive depression, with particularly high rates of comorbid anxiety and substance use disorders.² A recent study found that a significant number of patients who failed to respond to antidepressant medication may have undetected bipolar disorder.^{2,44}

The high rates of comorbid psychiatric conditions may also be related to the clinical population seen at the primary clinic where recruiting took place. As a tertiary psychiatry clinic, many patients

Table 3
Baseline Demographics and Clinical Characteristics of Participants.

Characteristic	Participants
Gender (%)	
Male	55
Female	44
BMI at Enrollment (kg/m ² ± SD)	33.0 ± 8.9
Average Age at Enrollment (years ± SD)	46.6 ± 11.6
Level of Education (%)	
high school or less	33
bachelor or collage	44
graduate or professional	11
Currently Employed (%)	
unemployed	44
part-time work	11
full-time work	22
other	11
Time since first depression episode (years ± SD)	17.3 ± 12.0
Taking antidepressant medication (%)	100
Concurrent anxiety disorder (%)	55
Average BDI Score at Enrollment (± SD)	18.6 ± 16.3
Minimal depression (BDI-II: 0–13) (%)	56
Mild depression (BDI-II: 14–19) (%)	0
Moderate depression (BDI-II: 20–28) (%)	22
Severe depression (BDI-II: 29–63) (%)	22
Average BAI Score at Enrollment (± SD)	13.6 ± 14.4
Minimal anxiety (BAI: 0–7) (%)	44
Mild anxiety (BAI: 8–15) (%)	33
Moderate anxiety (BAI: 16–25) (%)	11
Severe anxiety (BAI: 26–63) (%)	11
Baseline Serum 25-OHD (nmol/L ± SD)	50.6 ± 17.1

Table 4
Mean assessment tool scores and serum vitamin D levels at baseline and final visit.

Assessment Tool	Baseline (Mean ± SD)	Final (Mean ± SD)
BDI	18.6 ± 16.3	14.78 ± 12.19
BAI	13.6 ± 14.4	12.9 ± 17.4
IUS	80.9 ± 29.2	94.0 ± 33.7
FCPCS	130.6 ± 29.8	138.1 ± 40.5
SDS	15.2 ± 8.4	11.6 ± 9.9
Serum Vitamin D (nmol/L)	50.6 ± 17.1	83.3 ± 18.1

referred to the clinic have multiple psychiatric diagnoses. Recruiting from a primary care setting may allow for a greater numbers of respondents without comorbidities.

Additionally, the combination of this patient population with a placebo arm may have contributed to the recruitment difficulty. Since this population was already dealing with a long duration of illness and had failed to see benefit from one treatment, we hypothesize that they may have been less tolerant of potential enrollment in the inactive placebo arm and a lack of additional treatment for 3 months. Another clinical trial, although in a unique patient population, found this to be the case in individuals who failed previous interventions.⁴⁵

The factor that resulted in exclusion of the highest number of potential participants was the requirement for using one psychiatric medication as many individuals were taking no medications, multiple medications, low doses of medication or recently changed prescriptions. The high rates of these cases may be related to the non-remitted depression populations as a result of comorbidities, relapsing and remitting symptoms and sequential additions of therapies in response to failure to remit.

One additional challenge faced by the study was the limited funding available to studies assessing natural health products. A lack of honorarium for time and travel was cited by many individuals as the reason for declining screening or participation. Funding also limited the amount of advertisements needed to reach potentially eligible individuals. A recent study assessed motivation factors for healthy volunteers to participate in a randomized trial and found that 87.6% were

motivated to support medical research while, lack of financial compensation was reported by a minority of individuals as a reason for declining to participate.⁴⁶ A small study that explored the motivations of patients with depression found that a desire to help others or further science was reported most frequently.⁴⁷ While this suggests that motivation to participate may not be primarily dependent on financial compensation, the frequency with which this concern was cited by potential candidates suggests that this may be a factor that warrants consideration although additional practical and ethical considerations arise regarding participant remuneration and payment for participating in clinical trials.⁴⁸

The study was designed to have individuals participate during the winter months when vitamin D levels are lowest.⁴⁰ in order to increase the likelihood of observing a benefit from increasing serum levels through supplementation. Additionally, concern about time of year as a confounding variable in the study led to this decision. However, starting and stopping the study annually posed difficulty. Some patients contacted the study outside of the recruiting season or too close to the end of the season to allow time to complete the study but were no longer able to be reached, were no longer interested, or no longer qualified when recruiting resumed. A 2011 Canadian study found an average difference of only 6nmol/L between summer and winter.⁴⁰ This may be related to poor synthesis due to skin pigmentation in some individuals or limited summer sun exposure or to lifestyle factors that increase endogenous production during the winter months such as use of tanning beds or travel to Southern vacation locations which are noted to be common among Canadians.⁴⁰ Although this finding warrants confirmation, it suggests that the season may not have as large an impact as investigators may think and the benefit of year-round recruitment might be considered to enhance study feasibility. Subgroup analysis based on season of enrollment or use of a statistical model to estimate the contribution of sun exposure to participant vitamin D levels may be employed or considered in future studies.

The recruitment and enrollment challenges faced by this study may have been related to one of the above factors or a combination of factors. Future studies may benefit from our experiences in design and conduct of research. Because many patients are already choosing to supplement vitamin D or have already been prescribed this treatment, designing a protocol that allows for inclusion of these individuals may be beneficial for recruitment. A recent Canadian study found that while the prevalence of vitamin D deficiency in nonusers of vitamin D supplements was double the rate in supplement users (30.4% compared to 15.4%), the users still had a significant rate of deficiency. Designing a trial which accepts patients already using vitamin D but not achieving an optimal target value may be a feasible option. This methodology was used by another Canadian study which recruited patients based on low serum levels of vitamin D and did not enquire about intake of supplements.²¹ Alternately a four-arm study could be designed in which patients with adequate or inadequate vitamin D are randomized to receive either vitamin D or placebo. No studies assessing the role of vitamin D in depression have elucidated the respective roles of current supplementation compared to serum adequacy. This issue is further confounded by emerging research involving genetic polymorphisms associated with the vitamin D receptor, vitamin D (in)sufficiency, and the potential to influence development or successful treatment approaches in depression.^{49–51}

A recent study conducted by a Canadian university aggregated data from 14,000 participants on the effects of supplement dosage on serum vitamin D concentrations. They found that the daily dose needed for 97.5% of the population to achieve a serum level of at least 50 nmol/L was 2909 IU.⁵² Many patients currently taking vitamin D supplements are taking much lower doses, as suggested by the guidelines cited above and a study that employs a higher dose in order to significantly increase serum status may be warranted. A study comparing low and high dose vitamin D supplementation, as used in another study,²¹ could allow for inclusion of individuals already supplementing with low doses and

avoid the deterrent of potential randomization to the placebo arm.

Preference trials may be employed to account for the preferences both for and against vitamin D that were evident in the population screened. This type of trial could compare adjunctive vitamin D to conventional psychiatric management with sequential pharmacologic agents. This may allow recruitment of individuals not interested in vitamin D supplementation as part of the control group and decrease the deterring effect of possible placebo allocation in those interested in vitamin supplementation.

Other clinical trials assessing vitamin D in patients with depression have been able to recruit adequate numbers of participants however many of these utilized broader clinical populations, healthy subjects or health professionals. One study, which also employed vitamin D as an adjunct therapy to psychopharmacology, randomized patients diagnosed with MDD to either fluoxetine or fluoxetine plus vitamin D,¹³ This allows for study of the nutrient as an adjunctive therapy without utilizing a non-remitted depression population to avoid some of the challenges of high comorbidities, recent medication changes or multiple psychiatric medications.

This report has a number of limitations. While we are able to report on the reasons for not qualifying or declining participation, we can only report these for the individuals who responded to our advertisements or were able to be contacted. Individuals who chose not to contact the study for any of the reasons discussed above could not be accounted for. Additionally, when individuals were screened for eligibility, the phone screen was completed until the individual provided a response that made them ineligible. As such, individuals may have had multiple reasons for failing to qualify but only the first in the sequence of questions is reported. Questions asked early in the screen included willingness to participate without compensation, age, current medication, vitamin D supplementation; these may be over-represented in the reasons for failing to qualify. The later part of the phone screen assesses for comorbidities; these may be under-represented in our data.

5. Conclusions

The role of vitamin D as a therapeutic agent in the treatment of non-remitted major depressive disorder shows promise but continues to be unknown. This study highlights some of the challenges of this intervention and study population and may provide guidance in the design and conduct of other similar studies in the future to increase the likelihood of successful recruitment and enrolment in order to answer this important clinical question.

Conflicts of interest

None.

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References

- Sinyor M, Schaffer A, Levitt A. The sequenced treatment alternatives to relieve depression (STAR*D) trial: a review. *Can J Psychiatry Revue canadienne de psychiatrie*. 2010;55(March (3)):126–135 [PubMed PMID: 20370962].
- Rizvi SJ, Grima E, Tan M, et al. Treatment-resistant depression in primary care across Canada. *Can J Psychiatry Revue canadienne de psychiatrie*. 2014;59(July (7)):349–357 [PubMed Central PMCID: 4086317].
- Dold M, Kasper S. Evidence-based pharmacotherapy of treatment-resistant unipolar depression. *Int J Psychiatry*. 2017;21(March (21)):13–23 [PubMed PMID: 27848269].
- Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the

- management of adults with major depressive disorder: section 3. pharmacological treatments. *Can J Psychiatry Revue canadienne de psychiatrie*. 2016;16(September (9)):540–560 [PubMed Central PMCID: 4994790].
- Inderjeeth CA, Nicklason F, Al-Lahham Y, et al. Vitamin D deficiency and secondary hyperparathyroidism: clinical and biochemical associations in older non-institutionalised Southern Tasmanians. *Aust N Z J Med*. 2000;30(April (2)):209–214 [PubMed PMID: 10833112].
- Shipowick CD, Moore CB, Corbett C, Bindler R. Vitamin D and depressive symptoms in women during the winter: a pilot study. *Appl. Nurs Res: ANR*. 2009;22(August (3)):221–225 [PubMed PMID: 19616172].
- Groves NJ, McGrath JJ, Burne TH. Vitamin D as a neurosteroid affecting the developing and adult brain. *Annu Rev Nutr*. 2014;34:117–141 [PubMed PMID: 25033060].
- Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. *J Chem Neuroanat*. 2005;29(1(January (1))):21–30 [PubMed PMID: 15589699].
- Allan GM, Cranston L, Lindblad A, et al. Vitamin D: a narrative review examining the evidence for ten beliefs. *J Gen Intern Med*. 2016;31(July (7)):780–791 [PMID: 26951286. Pubmed Central PMCID: 4907952].
- Khamba BAM, Tsigielis D, Szpindel M, Laidlaw B, Epstein I, Katzman M. Effectiveness of Vitamin D in the treatment of mood disorders: a literature review. *J Orthomol Med*. 2011;26(3):127.
- Ju SY, Lee YJ, Jeong SN. Serum 25-hydroxyvitamin D levels and the risk of depression: a systematic review and meta-analysis. *J Nutr Health Aging*. 2013;17(5):447–455 [PubMed PMID: 23636546].
- Sepehrmanesh Z, Kolahdooz F, Abedi F, et al. Vitamin D supplementation affects the Beck depression inventory, insulin resistance, and biomarkers of oxidative stress in patients with major depressive disorder: a randomized, controlled clinical trial. *J Nutr*. 2016;146(February (2)):243–248 [PubMed PMID: 26609167].
- Khoraminy N, Tehrani-Doost M, Jazayeri S, Hosseini A, Djazayeri A. Therapeutic effects of vitamin D as adjunctive therapy to fluoxetine in patients with major depressive disorder. *Aust N Z J Psychiatry*. 2013;47(March (3)):271–275 [PubMed PMID: 23093054].
- Kjaergaard M, Waterloo K, Wang CE, et al. Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: nested case-control study and randomised clinical trial. *Br J psychiatry*. 2012;201(November (5)):360–368 [PubMed PMID: 22790678].
- Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose vitamin D3 and mental well-being: randomised controlled trial. *Br J Psychiatry*. 2011;198(May (5)):357–364 [PubMed PMID: 21525520].
- Dean AJ, Bellgrove MA, Hall T, et al. Effects of vitamin D supplementation on cognitive and emotional functioning in young adults—a randomised controlled trial. *PLoS One*. 2011;6(11):e25966 [PubMed PMID: 22073146. Pubmed Central PMCID: 3208539].
- de Koning EJ, van Schoor NM, Penninx BW, et al. Vitamin D supplementation to prevent depression and poor physical function in older adults: study protocol of the D-Vitaal study, a randomized placebo-controlled clinical trial. *BMC Geriatr*. 2015;19(November (15)):151 [PubMed PMID: 26585952. Pubmed Central PMCID: 4653865].
- Lansdowne AT, Provost SC. Vitamin D3 enhances mood in healthy subjects during winter. *Psychopharmacology (Berl)*. 1998;135(February (4)):319–323 [PubMed PMID: 9539254].
- Frandsen TB, Pareek M, Hansen JP, Nielsen CT. Vitamin D supplementation for treatment of seasonal affective symptoms in healthcare professionals: a double-blind randomised placebo-controlled trial. *BMC Res Notes*. 2014;14(August (7)):528 [PubMed Central PMCID: 4141118].
- Wang Y, Liu Y, Lian Y, Li N, Liu H, Li G. Efficacy of high-Dose supplementation with oral vitamin D3 on depressive symptoms in dialysis patients with vitamin D3 insufficiency: a prospective, randomized, double-Blind study. *J Clin Psychopharmacol*. 2016;36(June (3)):229–235 [PubMed PMID: 27022679].
- Vieth R, Kimball S, Hu A, Walfish PG. Randomized comparison of the effects of the vitamin D3 adequate intake versus 100 mcg (4000 IU) per day on biochemical responses and the wellbeing of patients. *Nutr J*. 2004;19(July (30)):8 [PubMed PMID: 15260882. Pubmed Central PMCID: 506781].
- Shaffer JA, Edmondson D, Wasson LT, et al. Vitamin D supplementation for depressive symptoms: a systematic review and meta-analysis of randomized controlled trials. *Psychosom Med*. 2014;76(April (3)):190–196 [PubMed PMID: 24632894. Pubmed Central PMCID: 4008710].
- Arnau RC, Meagher MW, Norris MP, Bramson R. Psychometric evaluation of the Beck Depression Inventory-II with primary care medical patients. *Health Psychol*. 2001;20(March (2)):112–119 [PubMed PMID: 11315728].
- Beck SR AT, Brown GK. *Beck Depression Inventory Manual*. 2nd ed. Psychological Corporation; 1996.
- Buhr K, Dugas MJ. The Intolerance of Uncertainty Scale: psychometric properties of the English version. *Behav Res Ther*. 2002;40(August (8)):931–945 [PubMed PMID: 12186356].
- Buhr K, Dugas MJ. Investigating the construct validity of intolerance of uncertainty and its unique relationship with worry. *J Anxiety Disord*. 2006;20(2):222–236 [PubMed PMID: 16464706].
- Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol*. 1988;56(December (6)):893–897 [PubMed PMID: 3204199].
- Beck ATSR, Brown GK. *Beck Anxiety Inventory Manual*. The Psychological Corporation Harcourt Brace Jovanovich Inc.; 1990.
- Osman A, Kopper BA, Barrios FX, Osman JR, Wade T. The Beck Anxiety Inventory: reexamination of factor structure and psychometric properties. *J Clin Psychol*. 1997;53(January (1)):7–14 [PubMed PMID: 9120035].

30. Leventhal AM, Chasson GS, Tapia E, Miller EK, Pettit JW. Measuring hedonic capacity in depression: a psychometric analysis of three anhedonia scales. *J Clin Psychol.* 2006;62(December (12)):1545–1558 [PubMed PMID: 17019674].
31. Franken IH, Rassin E, Muris P. The assessment of anhedonia in clinical and non-clinical populations: further validation of the Snaith-Hamilton Pleasure Scale (SHAPS). *J Affect Disord.* 2007;99(April (1–3)):83–89 [PubMed PMID: 16996138].
32. D'Haenen H. Measurement of anhedonia. *Eur Psychiatry.* 1996;11(7):335–343 [PubMed PMID: 19698477].
33. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M. I. N. I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry.* 1998;59(Suppl. 20):22–33 [quiz 4–57. PubMed PMID: 9881538].
34. George MS, Rush AJ, Marangell LB, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol Psychiatry.* 2005;58(5):364–373 [Sep 01 PubMed PMID: 16139582].
35. Alshahrani F, Aljohani N. Vitamin D: deficiency, sufficiency and toxicity. *Nutrients.* 2013;5(9):3605–3616 [Sep 13. Pubmed Central PMCID: 3798924].
36. Dickert NW, Halpern SD, Butler J. Incentivizing recruitment and retention to address enrollment challenges in clinical research. *Circ Cardiovasc Qual Outcomes.* 2013;6(3):367–370 [May 01. PubMed PMID: 23652736].
37. Bouillon R. Comparative analysis of nutritional guidelines for vitamin D. *Nat Rev Endocrinol.* 2017(April (07)) [PubMed PMID: 28387318].
38. Papaioannou A, Morin S, Cheung AM, et al. clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. *CMAJ: Can Med Assoc J.* 2010;182(17):1864–1873 [Nov 23. Pubmed Central PMCID: 2988535].
39. Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst Rev.* 2014;10(January (1)) [CD007470. PubMed PMID: 24414552].
40. Whiting SJ, Langlois KA, Vatanparast H, Greene-Finestone LS. The vitamin D status of Canadians relative to the Dietary Reference Intakes: an examination in children and adults with and without supplement use. *Am J Clin Nutr.* 2011;94(July (1)):128–135 [PubMed PMID: 21593503].
41. Gaul C, Malcherczyk A, Schmidt T, Helm J, Haerting J. Motivation of patients to participate in clinical trials. An explorative survey. *Med Klin.* 2010;105(February (2)):73–79 [PubMed PMID: 20174906. Bereitschaft von Patienten zum Einschluss in klinische Studien: Eine explorative Studie.].
42. *Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary.* Washington (DC): The National Academies Collection: Reports funded by National Institutes of Health; 2010.
43. Kanai T, Takeuchi H, Furukawa TA, et al. Time to recurrence after recovery from major depressive episodes and its predictors. *Psychol Med.* 2003;33(July (5)):839–845 [PubMed PMID: 12877398].
44. Sernat TFK, Fine A, Cameron C, Epstein I, Katzman MA. Trait anhedonia a risk factor for undetected attention deficit hyperactivity disorder and suicide in adult depressed patients. *Presented at the World Congress of ADHD.* 2017.
45. Trussell JC, Christman GM, Ohl DA, et al. Recruitment challenges of a multicenter randomized controlled varicocelelectomy trial. *Fertil Steril.* 2011;96(December (6)):1299–1305 [PubMed PMID: 22130101. Pubmed Central PMCID: 3243664].
46. Luzurier Q, Damm C, Lion F, Daniel C, Pellerin L, Tavolacci MP. Strategy for recruitment and factors associated with motivation and satisfaction in a randomized trial with 210 healthy volunteers without financial compensation. *BMC Med Res Methodol.* 2015;05(January (15)):2 [PubMed PMID: 25559410. Pubmed Central PMCID: 4293827].
47. Andresen EL, Wilson KA, Castillo A, Koopman C. Patient motivation for participating in clinical trials for depression: validation of the motivation for clinical trials inventory-depression. *Int Clin Psychopharmacol.* 2010;25(January (1)):7–16 [PubMed PMID: 19901843].
48. Grady C. Payment of clinical research subjects. *J Clin Invest.* 2005;115(July (7)):1681–1687 [Pubmed Central PMCID: 1159153].
49. Kuningas M, Mooijjaart SP, Jolles J, Slagboom PE, Westendorp RG, van Heemst D. VDR gene variants associate with cognitive function and depressive symptoms in old age. *Neurobiol Aging.* 2009;30(March (3)):466–473 [PubMed PMID: 17714831].
50. Wang TJ, Zhang F, Richards JB, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. *Lancet.* 2010;376(9736):180–188 [Jul 17. Pubmed Central PMCID: 3086761].
51. Dastani Z, Li R, Richards B. Genetic regulation of vitamin D levels. *Calcif Tissue Int.* 2013;92(February (2)):106–117 [PubMed PMID: 23114382].
52. Veugelaers PJ, Pham TM, Ekwaru JP. Optimal Vitamin D supplementation doses that minimize the risk for both low and high serum 25-Hydroxyvitamin d concentrations in the general population. *Nutrients.* 2015;7(12):10189–10208 [Dec 04. Pubmed Central PMCID: 4690079].