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.  
A recent Canadian study found that 22% of a large sample of depressive patients failed to respond to at least two consecutive antidepressant agents. 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.  
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. New research suggests that deficiency of vitamin D may have an impact on mood, primarily through an effect on neurotransmitters. Vitamin D is a neurosteroid, capable of crossing the blood-brain barrier, with physiological effects on neuroprotection, neuromodulation, brain development, and regulation of neurotrophic factors. 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. 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.  
Numerous observational studies suggest a relationship between low levels of vitamin D and increased incidence and severity of mood disorders. 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. 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, inadequate control and blinding, non-clinically depressed patient populations, a diagnosis of seasonal affective disorder, the presence of other comorbidities, and use of assessment tools lacking validation 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. 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
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