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Is Oral Vitamin D Supplementation Safe and Effective for Adults as Therapy to Improve Symptoms Associated with Seasonal Affective Disorder (SAD) during Wintertime?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not oral vitamin D supplementation is safe and effective for adults as therapy to improve symptoms associated with seasonal affective disorder (SAD) during wintertime.

Study Design: This review is based on three randomized controlled trials (RCTs) which were published in 2006, 2012, 2014. Two of the studies were double blind and placebo controlled. The studies evaluated the efficacy of oral vitamin D supplementation for improvement of seasonal affective disorder (SAD) symptoms. One of the studies also evaluated safety.

Data Sources: All articles used were published in English, in peer-reviewed journals and found in PubMed during the time period of November 2015 to February 2016.

Outcomes Measured: The outcomes measured were symptoms associated with SAD. One study measured subjective psychological well-being qualities (energy and vitality, social functioning, role functioning, and mental health), which were measured by Mean Component Score (MCS). The other two studies evaluated symptoms associated with SAD and perceived change from normal in: length of sleep, social activities, mood, weight, appetite, energy level by using Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorders (SIGH-SAD) and Global Seasonality Score (GSS) tools.

Results: None of the studies evaluated in this review had results to suggest that vitamin D supplementation is effective for improving symptoms associated with SAD. Dumville (2006) found no significant evidence ($p = 0.262$). Frandsen (2014) and Kjaergaard et al. (2012) both found no significant difference between placebo and vitamin D with p values of 0.7 and 0.734 respectively. Kjaergaard et al. (2012) also found there to be no significant difference in adverse events between the placebo and vitamin D groups.

Conclusions: This review suggests that although oral vitamin D supplementation is safe, it is not effective for adults as therapy to improve symptoms associated with SAD during wintertime.

Keywords: vitamin D, seasonal depression, adults

Introduction

Seasonal Affective Disorder (SAD) is a seasonal pattern of depression with onset and remission at predictable times of year.[1] The hallmark symptoms include: fatigue, weight gain, lack of energy, hypersomnia, and episodic carbohydrate craving.[1] It is more common in women and at higher latitudes.[1] Most people with SAD experience symptoms that start in the fall and continue into winter.[2] The mainstay of treatment for SAD at this time includes light therapy, psychotherapy, and medications.[2] This paper evaluates three randomized controlled trials, two of which were double blind placebo controlled, investigating whether vitamin D supplementation is safe and effective as treatment for SAD symptoms.

While not as prevalent as major depressive disorder, SAD is still common. In 2009-2010 there were approximately eight million ambulatory visits for depression including those with SAD.[3] About 5% of the US population experiences SAD in a given year with symptoms lasting approximately 40% of the year.[4] Symptoms of SAD can be severe and may cause significant impairment of a person's ability to function normally at work, school, or home.[4] Furthermore, it is a condition that is frequently encountered in primary care and may be easily overlooked or downplayed as simply being "under the weather". According to the medical resource UpToDate, SAD affects 5-10% of primary care patients and 15% of depressed patients.[5] This represents a significant demand of time by clinicians and money on the healthcare system as a whole. The economic burden of treating SAD in particular is not known, however, when it is considered together with the cost of treating major depression in the United States it was estimated to be a staggering $210.5 billion in 2010 and has been increasing.[6]

As one might expect, depression has been shown to negatively affect patients' social relationships and performance at work or school.[7] In this way, if depression or SAD is left

untreated then it may have a significantly negative impact on patients' overall wellness. Not only does depression affect self-reported metrics of wellness and quality of life, but it has also been shown to negatively influence objective measures of health status.[8] One of the ways that depression, and presumably mental illness in general, may affect one's health or wellness status is through noncompliance. Depressed patients are three times more likely to be noncompliant with medical treatment recommendations.[9] Clinicians need to be vigilant in recognizing and treating depression symptoms if they are to truly provide high quality medical care.

The underlying pathophysiology and etiology of SAD and depression is unknown, however, it is believed that several different biological, psychological, and environmental mechanisms are involved.[10] A large portion of these mechanisms reflect neuroendocrine abnormalities. These include: increased cortisol and corticotropin releasing hormone, increase in adrenal size, decreased inhibitory response of glucocorticoids to dexamethasone, a blunted response of thyroid stimulating hormone to thyroid releasing hormone, and an increase in inflammatory cytokines.[1] From a biological perspective, it has been demonstrated that diurnal variations in symptoms correlate with changes in circadian rhythm and neurotransmitters, which suggests that a dysregulation of biologic rhythms may also play a role.[1] SAD in particular is thought to be associated with reduced levels of sunlight in fall and winter, thereby causing disruptions in circadian rhythm, levels of serotonin and melatonin, and manifesting as alterations in mood and symptoms of depression.[11]

At this time, the first line treatments for SAD include light therapy of two hours at 2500 lux or 30 minutes at 10,000 lux every day, or antidepressant medication (SSRIs) like fluoxetine 10 mg every day.[12] Light therapy has been shown to be effective, however, not without a few drawbacks. Compliance and consistency are crucial to achieve the full benefit of therapy, and

due to the possible side effects like headache, eye strain, and agitation, it is recommended that it only be used under the supervision of a mental health professional.[7] For many patients, the time and schedule commitment as well as the associated monetary cost to the patient of frequent office visits may prove to be impractical. Vitamin D has been hypothesized as a potential treatment option for SAD because of research that has implicated its role in depression, low cost, and the convenience of oral supplementation.[13] Vitamin D, or more specifically cholecalciferol (D3), is a neurosteroid hormone that is involved with many brain processes such as neuroimmunomodulation, neuroprotection, neuroplasticity, and brain development.[13] Low levels of vitamin D are associated with depression and also prevalent during the winter months, making it a prime candidate to pursue as a therapy option for SAD symptoms.

Objective

The objective of this selective EBM review is to determine whether or not oral vitamin D supplementation is safe and effective for adults as therapy to improve symptoms associated with seasonal affective disorder (SAD) during wintertime.

Methods

This review evaluates three randomized controlled trials, two of which were double blind and placebo controlled. Studies were selected based on their relevance to this review's objective and according to specific criteria including: the target population, types of interventions used, comparisons made, and the outcomes measured. All three of the studies included the target population of adults over 18 years old, in some form. Dumville[14] studied women over 69 years, Frandsen[15] studied adults ages 18-65 years old, and Kjaergaard et al.[16] studied adults ages 30-65 years old.

All of the studies used oral vitamin D supplementation as their intervention. Dumville

used Calcichew D3 forte tablets - two tablets per day were taken orally providing a daily total of 1000mg calcium and 800IU vitamin D for 6 months from November to April.[14] Frandsen used a daily dose of 70 μg vitamin D x 12 weeks.[15] Kjaergaard et al. used vitamin D3 capsules (20,000 IU cholecalciferol) x 2 per week x 6 months.[16] Two of the studies compared the intervention groups versus placebo control groups and one study compared the intervention group versus a no intervention group. The outcomes that were measured in all of the studies were symptoms associated with SAD such as changes in mental well-being, social activity, mood, appetite, and energy level. The ways in which the outcomes were measured differed from study to study and the details are described in the Outcomes Measured section of this review.

The author performed searches for the articles in PubMed during the time period from 11/23/15 to 2/26/16. The articles were found using the following key words in search queries: vitamin d, seasonal depression, and adults. All of the articles were published in English and collected from peer reviewed journals. The articles were selected based on their relevance to this review's clinical question and whether or not they included the target patient oriented outcomes (POEM). Inclusion and exclusion criteria were also used in order to focus the article selection process. The inclusion criteria were simply that each article had to be a randomized controlled trial. If the article included patients under the age of 18 years old, then it was excluded from consideration for this review. The inclusion and exclusion criteria that were employed in each specific study are included in Table 1 below. Many different statistics were reported or used in the selected articles including: difference of mean change from baseline, p value, confidence interval (CI), mean change from baseline, median, range, delta, and numbers needed to harm (NNH). A p value was provided in all of the studies, while a NNH value was only provided in Kjaergaard et al.[16] See Table 1 below for the demographics and characteristics of the included

studies.

Table 1: Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Dumville[14] (2006)	RCT	2117	≥ 70	Women ≥70 years old, took < 500 mg of supplemental Ca daily, did not have bladder or kidney stones and had one or more risk factors	A life expectancy of <six months, or if they had cognitive impairments	496	Calcichew D3 forte tablets - 2 tablets PO QD providing a daily total of 1000mg calcium and 800IU vitamin D for 6 months from November to April.
Frandsen[15] (2014)	Double blind RCT	50	18-65	Healthcare worker in the region of Southern Denmark, 18– 65 years old, and had moderate symptoms associated with SAD	Any form of schizophrenia, bipolar affective disorder, sarcoidosis, tuberculosis and pregnancy, or an intake of more than 10 μg vitamin D per day. Serum lab value criteria for Vit D, Ca, PO, and PTH were also used	14	Daily dose of 70 μg vitamin D x 12 weeks
Kjaergaard et al.[16] (2012)	Double blind RCT	237	30-75	Serum 25(OH)D levels found to be below the 20th percentile in the sixth Tromso study conducted between 2007 and 2008.	Patients with comorbidities, fertile women not using contraception, taking vitamin D supplements or mood altering medication, possible hyperparathyroidism, or severe depression	7	Vitamin D3 capsules (20,000 IU cholecalciferol) x 2 per week x 6 months

Outcomes Measured

Dumville measured symptoms of SAD by using a Mental Component Score (MCS) tool which was used to assess participants' self-reported psychological well-being at baseline (November) and at six months (April).[14] This score was based on four categories of a more comprehensive health related quality of life questionnaire known as the SF-12. The four categories considered were: energy and vitality, social functioning, role functioning (emotional), and mental health.

Frandsen measured symptoms of SAD as a recorded score from the self-reported questionnaire Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorders (SIGH – SAD).[15] The SIGH-SAD is a 24 item scripted version of the Hamilton Depression Rating Scale that was modified to better reflect the characteristic symptomatology of SAD. Assessments were performed at baseline (January) and at 12 weeks (March) later.

Kjaergaard et al. studied the perceived change from normal in six categories of symptoms related to SAD: length of sleep, social activities, mood, weight, appetite, and energy level.[16] This was performed by using Global Seasonality Score (GSS) - a sum total score based on responses from the Seasonal Pattern Assessment Scale (SPAQ) questionnaire. In the SPAQ, participants rated the change that they experienced in each of the six categories from 0 to 4, with a 0 indicating no change and a 4 indicating a great change. Assessments were performed at baseline (October) and after six months (April).

Results

In the Dumville RCT, a total of 2117 women were recruited to the trial from primary care in three areas of the UK.[14] This was done according to the inclusion and exclusion criteria

previously described in Table 1. 9% of the subjects were smokers. The target population was chosen based on the hypothesis that SAD is linked to vitamin D deficiency; a common problem among the elderly and during the winter months. Two groups were assigned randomly - a control group made of 1205 women and an intervention group made of 912 women. The intervention group was given calcium and vitamin D supplementation (detailed in the Methods section) while the control group did not. Adherence to treatment was not explicitly mentioned. Baseline measures were taken between the months of May and October according to the methods described in the Outcomes Measured section. Of these women, only 1621 (77%) had an SF-12 score deemed to be valid (more than 5 items completed) both at baseline and six months and were considered for further analysis through Mental Component Scoring (MCS). Results were analyzed using SPSS 11, all analysis was done on an intention to treat basis, and the relationship between vitamin D supplementation and six month MCS score was assessed using ANCOVA adjusting for score at baseline and age. A summary of results can be seen in Table 2.

Table 2 – Difference in mean MCS scores for control and treatment groups at 6 months

Difference between control and treatment six month scores after controlling for baseline score and age	P value	Confidence Interval (CI)
-0.49	0.262	(-1.34 – 0.81)

This study demonstrates that after six months of intervention with 800 IU of vitamin D supplementation daily, the intervention group of elderly women experienced no significant improvement in their Mental Component Score, a reflection of their mental health and symptoms associated with SAD. The p value of 0.262 is well out of the statistically significant threshold of <0.05, making these results not significant.

In the Frandsen double-blind, placebo controlled, RCT, 3345 healthcare professionals from hospitals in Southern Denmark were invited to participate.[15] 50 participants were screened

by a research nurse. Seven were excluded before randomization according to the inclusion and exclusion criteria described in Table 1, and of the remaining 43 included in the trial, only 34 were eventually able to complete the entire study. The main inclusion criteria were adults age 18-65 with the presence of moderate SAD symptoms as determined by a score of 8 points or more on question 2 of the Seasonal Pattern Assessment Questionnaire, Seasonal Affective Disorders (SPAQ-SAD). Participants were randomized to a treatment group (22 people) which received 70 micrograms of vitamin D daily or a controlled group (21 people) that received placebo daily for a period of 12 weeks during the winter period. The primary outcome that was assessed was the sum of the self-reported SIGH-SAD. This assessment was performed at baseline and at 12 weeks after baseline. Known side effects of vitamin D supplementation including: fatigue, muscle spasm, pain, nausea, constipation, as well as severe/adverse events were also recorded at baseline and 12 weeks. Treatment adherence was accounted for by counting the returned pills after 12 weeks. The analyses were conducted on an intention to treat basis. All of the subjects who entered into the trial were accounted for at the conclusion, however, 23% were lost to follow up. A summary of results is included below in Table 3.

Table 3 – Mean change from baseline after 12 weeks for treatment and control groups

	Mean change from baseline	Standard Deviation
Treatment Group	-6.4	7.3
Control Group	-6.8	9.5

The p value of the primary outcome was not significant at 0.7 and the confidence interval was -3.27 to 4.81. Additionally, there were no significant differences between treatment and control groups at baseline. There was significant improvement of SIGH-SAD scores for all participants from baseline to the conclusion of the study. All analyses were completed using STATA/IC 11 software. Treatment adherence was high at 85.9%. There were no significant

differences between groups for known side effects or adverse events from vitamin D supplementation.

In the Kjaergaard et al. double-blind, placebo controlled, RCT, a nested case control study was performed evaluating adults 30-75 years old for serum vitamin D levels in Tromso, Norway.[16] Individuals with low levels, according the inclusion and exclusion criteria described in Table 1, were then invited to participate in an interventional study whereby 243 participants were randomized to a control and treatment group. A total of 230 participants actually completed the study. The treatment adherence rate was 94%. At baseline there were no differences among control and treatment groups. Treatment group received vitamin D3 capsules (20,000 IU cholecalciferol) x 2 per week x 6 months, and the control group received placebo x 2 per week x 6 months. Assessment for outcomes was done at baseline (October 2009) and after six months (April 2010). Data was analyzed using a per protocol approach and an intention to treat approach. Subjects lost to follow up were analyzed by using a last observation carried forward method thus giving participants who did not complete the study a change in depression score of zero. Statistical analyses were performed using PASW. Four primary outcomes were measured, of which only the self-reported Global Seasonality Score (GSS) was considered for this review. Respiratory harm from intervention was also reported. A summary of results can be viewed in Table 4.

Table 4 – Change in median GSS at 6 months minus score at baseline (delta)

	Delta	Range
Treatment group	-0.72	3.4
Control group	-0.28	4.66

The p value for delta was found to be non-significant at 0.734. There was also no significant difference in adverse events between the treatment and control groups. Table 5 below shows data for respiratory adverse events during the 6-month intervention period, which was the

most common adverse event detected in both control and treatment groups overall. Table 6 below shows the calculated measures of harm from placebo versus vitamin D treatment groups for respiratory adverse events.

Table 5 – Respiratory adverse events during the intervention period between groups

	Placebo (n=121)	Vitamin D (n=122)
Respiratory	61	67

Table 6 – Calculated measures of harm for respiratory adverse events

Control event rate (CER)	Experimental event rate (EER)	Relative risk increase (RRI)	Absolute risk increase (ARI)	Number needed to harm (NNH)
50.4%	54.9%	8.93%	4.5%	23

The Kjaergaard et al. trial was the only one of the studies chosen for this review that evaluated safety and adverse events from the intervention of vitamin D supplementation. The CER and EER show that roughly 50 – 55% of the patients in the treatment and control groups experienced adverse respiratory events during the trial, and at equal proportions. The NNH of 23 indicates that for every patient given vitamin D supplementation, one will likely have an adverse respiratory event when compared to the control.

Discussion

While the overwhelming results of the three studies used in this review do not provide any significant evidence to suggest that vitamin D is an effective therapy for improving symptoms of SAD, each study had specific limitations which may have affected their results. Dumville used a population at risk for SAD – elderly women, with low vitamin D levels, living at a high latitude during the winter – but the actual presence of SAD in the trial population was never measured.[14] The treatment and control groups did however have similar SF-12 scores at baseline. Dumville also admits that in their study they did not see the expected seasonal decline in mental health scores that would be expected if a large proportion of their subjects actually had SAD.[14] Furthermore, the study population of elderly women are indeed adults eligible for this

review but their reflection of adults in general is limited. Frandsen admits that their treatment effect could have been diminished by not including low vitamin D patients at baseline (higher risk for SAD) or requiring patients to have a higher SAD severity for inclusion.[15] Also, their sample size was small and the study could have been subject to type II error. The main limitation of the Kjaergaard et al. study was similar to Dumville in that they used a target population at risk of SAD without actually confirming the presence of it before intervention.[16] It is also plausible that six months is not long enough of a time frame to properly evaluate SAD, or that the vitamin D supplementation was at too high of a dose.[16]

Conclusion

None of the studies selected for this review provided any significant evidence that oral vitamin D supplementation is an effective means of improving or preventing symptoms associated with SAD in adults during wintertime. In Kjaergaard et al., they were able to show that patients with low vitamin D levels have higher depression scores, but they were not able to demonstrate that vitamin D supplementation conferred any improvement.[16] They propose that this may be due to the possibility that low vitamin D levels are a result of depression symptoms rather than a cause for it.[16] In regards to the safety of vitamin D supplementation, this review concludes that it is indeed safe based on the results of Kjaergaard et al. when used for treatment of depression or SAD symptoms and that the risk of adverse events is low.

Further studies are warranted to explore the relationships between vitamin D levels, brain function, and mental health. Future design methods may be improved by: confirming the presence of SAD symptoms at baseline prior to intervention, using a questionnaire tailored specifically for SAD, and using multiple treatment groups to cover a wide range of vitamin D supplementation dosages.

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