

Vitamin D for depression with a seasonal pattern: an effective treatment strategy

Abstract

Background: Low level of vitamin D is often associated with major depression with a seasonal pattern, formerly known as seasonal affective disorder under the DSM IV classification. Major depressive disorder is commonly observed during the fall and winter seasons in countries away from the tropical zone and is referred to as depression with a seasonal pattern under the DSM V classification. Here, we conduct a review of literature to address the factors highlighting the association between vitamin D level and depression with a seasonal pattern.

Objective: 1) Review the epidemiology, etiology and pathogenesis associating vitamin D level and depression. 2) Provide treatment recommendations and practice guidelines for addressing vitamin D deficiency associated with depression with a seasonal pattern.

Methods: Literature review on human studies published in English language from 2000-2017 using PubMed, EBSCO, and Google Scholar was performed.

Results: Majority of published studies have associated low level of vitamin D to depression with a seasonal pattern. A high prevalence of major depressive disorder is observed in Northern latitude countries with severe, prolonged winter that experience little or no sunshine available within the wavelength that is necessary for cutaneous synthesis of vitamin D. A review of literature indicated that reduced exposure to sunlight is associated with low levels of vitamin D, decreased serotonin activity, an increased production of melatonin, and changes in circadian rhythm. Associated factors include socio-demographic (older age, female, higher BMI>25Kg/m², geographical location), and clinical correlates including chronic pain, comorbid neuropsychiatric conditions, chronic diseases (hypertension, diabetes mellitus, autoimmune disorder), and musculoskeletal disorders. Treatment recommendations include light therapy, antidepressant treatment, psychotherapy, melatonin and vitamin D supplementation. Among all the modalities, vitamin D supplementation is an effective preventative and treatment strategy for the management of depression with a seasonal pattern.

Conclusion: Sunlight exposure within the recommended wavelength promotes vitamin D synthesis from cholesterol in the skin. Vitamin D deficiency is observed among adults especially those residing in sunlight deficient geographical locations. Among vitamin D deficient individuals suffering from major depression with a seasonal pattern, early detection and vitamin D supplementation can be a simple, convenient, and cost-effective treatment strategy for improving symptoms and mental health outcomes associated with major depression.

Keywords: vitamin D, depression, seasonal affective disorder, prevalence, treatment

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Introduction

Low level of vitamin D has been linked to the symptoms of recurrent major depression with a seasonal pattern.¹ Vitamin D is a fat soluble vitamin, also referred to as the sunshine vitamin obtained from natural sunlight exposure to skin.² Sunlight has the ultraviolet-B (UVB) photon rays that promote vitamin D synthesis under specific conditions from cholesterol in the skin.³ Apart from sunlight, diet (fatty fish, dairy products, egg yolk, beef liver) and vitamin D fortified food products (orange juice, cereals, etc.) are enriched nutritional sources of vitamin D.⁴ Seasonal affective disorder (SAD), in accordance with DSM V, has changed the classification status to recurrent major depressive disorder with a seasonal pattern, which is a variant of depression that occurs during fall and winter seasons, often referred to as winter blues or seasonal depression.^{5,6} Duration, frequency, and severity of these depressive disorders vary with geographical latitude,

temperature and climate.⁷ Depressive symptoms associated with low level of vitamin D include depressed mood, irritability, frequent crying spells, tiredness, social withdrawal, decreased energy levels, appetite and sleep disturbances.^{8,9} Atypical symptoms of depression including hypersomnia, carbohydrate craving, increased appetite, weight gain and extreme fatigue are also common.¹⁰ Similar to all depressive disorders, feelings of self-harm, suicidal ideation or tendencies are observed in individuals with major depression with a seasonal pattern.¹¹

Vitamin D and sunlight are effective not only in the management of depressive disorders but also are beneficial for comorbidities including prevention and treatment of osteoporosis, arthritis, autoimmune diseases, inflammatory bowel diseases (IBD), cardiovascular diseases, chronic diseases such as type 2 diabetes mellitus and certain forms of cancers.^{12,13} Therefore, the active form of vitamin D, referred to as

1,25-dihydroxycolecalciferol (vitamin D₃) is often used clinically for the prevention and treatment of specific health conditions.¹⁴ Here, we review the epidemiology, etiology and pathogenesis highlighting the association between vitamin D level and depression with a seasonal pattern. Additionally, treatment recommendation and practice guidelines for the management of vitamin D deficiency associated depression with a seasonal pattern is provided with an emphasis on vitamin D as an effective preventative and treatment strategy.

Methods

Online databases (PubMed, Medline, EBSCO, Psycinfo) along with articles from Google scholar were searched from 2000-2017. Only articles published in English language were included. Key reviews and original research articles for adult population were included using the terms “vitamin D”, “recurrent”, “major”, “depression”, “seasonal”, “pattern”, “seasonal affective disorder”, “symptoms”, “psychiatry”, “neuro-psychiatric”, “depressive disorder”, “etiology”, “prevalence”, “epidemiology”, “pathology”, “pathogenesis”, “clinical”, “practice”, “treatment”, “recommendations”, “guidelines”. These search terms were used in combination with each other using the conjunction “AND” and “OR”. The search was supplemented by a manual review of the reference list from relevant articles. The search yielded more than 400 articles. A total of 229 articles were included for the initial review. Articles were excluded for duplication, animal studies, laboratory or preclinical studies emphasizing on the molecular structure, physiology, biochemistry, pharmacokinetics or pharmacodynamics of vitamin D. Only, 129 articles that were recent and clinically relevant to the topic and subheadings were included in the final review.

Results

Epidemiology

Majority of published studies have associated low level of vitamin D to depressed mood and major depression with a seasonal pattern.¹⁵ Prevalence of depression with seasonal pattern is approximately 10% in Northern latitudes and ranges from 1.5-9% depending upon the latitude.¹⁶ In the general adult population, prevalence varies between 0.4-16% based on latitude, age, gender and other lifestyle factors.¹⁷ Prevalence reporting for specifically vitamin D deficiency associated depression with a seasonal pattern is difficult as the disorder often goes unreported or underreported and consequently undiagnosed.¹⁸

Systematic reviews and meta-analytic studies indicate lower vitamin D levels among patients suffering from depression compared with controls with increased odds ratio of depression for the lowest vs. highest vitamin D categories.¹⁹ One study specifically indicated that the depression prevalence increases with categorically low levels of vitamin D. For example., in a sample of older adults >65 years, prevalence of depressive symptoms was 22.6% with vitamin D-25(OH)D levels of <30 ng/mL (85.4%); prevalence of depression increased to 25.8% in participants with lower 25(OH)D levels of <20 ng/mL (51.4%); and a greater increase in the prevalence of depression noted to be 35% in participants with lowest 25(OH)D levels of <10ng/mL (9.8%).²⁰ Another study conducted by Spedding²¹ examined fifteen randomized controlled trials (RCT) that investigated the association of vitamin D level and depression and indicated that vitamin D supplementation ≥800 I.U daily is favorable in the management of depression.

Similarly, cohort studies indicate a significantly increased risk/hazard ratio of depression for the lowest vs. highest vitamin D categories.¹⁹ Conversely, one study found no association between vitamin D deficiency and depression among middle to elderly Chinese participants from Beijing and Shanghai.²² Epidemiologic studies associating vitamin D level and depression are mostly cross-sectional and provide mixed results. Due to the research methodological limitation including study design, sample size, lack of control of confounding factors and other issues; it is difficult to confidently interpret a significant causal association vs. a circumstantial evidence between vitamin D level and occurrence of depression.²³ Nevertheless, majority of the studies support an association between low levels of vitamin D and depression.

Etiology and pathogenesis

The exact mechanism involved in the etiology and pathogenesis of vitamin D and depression is not known. A review of literature indicated that reduced exposure to sunlight is associated with decreased serotonin activity, low vitamin D level in the body, an increased production of melatonin by melanocytes in the skin, and changes in circadian rhythm.^{24,25} One study reported that the duration of bright sunlight exposure is significantly correlated with serotonin production rate by the brain ($r=0.29$, $p=0.10$) that rises rapidly with increased luminosity and conversely, serotonin turnover by the brain is lowest in winter ($p=0.01$).²⁶ Altered regulation of neurotransmitter serotonin that maintains mood, specifically reported as enhanced 5-HTT (serotonin) transporter function along with seasonal fluctuations in brain serotonin binding receptor is observed among patients with depression with a seasonal pattern.²⁷ Depressed patients exhibit 5% more serotonin receptor transporter (SERT), in winter months than in summer.²⁸ Since SERT transports serotonin from the synaptic cleft to the presynaptic neuron, therefore, higher SERT levels lead to lower serotonin activity.²⁸ During summer, sunlight keeps SERT levels naturally low but in fall and winter season as sunlight diminishes, a corresponding reduced brain serotonin transporter availability and consequent decrease in serotonin activity occurs, as noted by imaging, thus causing low mood symptoms and depression.²⁹

Alteration in melatonin production affecting the normal biological circadian rhythm is often associated with depression with seasonal pattern.³⁰ Melatonin is also known as the darkness hormone and is produced by the pineal gland that responds to darkness by causing sleepiness consequently high levels of melatonin are found at night vs. low levels during daytime.³¹ During shorter days of winter, as days become darker, melatonin production increases and makes people sleepy and lethargic, affecting their circadian bio-physiological rhythms with altered sleep/wake cycle, thus causing some people to become depressed.²⁴

Circadian rhythms also known as the body's internal biological 24-hour clock are entrained to respond to rhythmic dark-light changes that occur at certain times during the day and in each season.³² Among people suffering from depression, the circadian signal that indicates a seasonal change in day length is timed differently that makes the individual physiological response mechanisms (sleep wake cycle, cortisol release and related metabolic system) difficult to adjust to the seasonal fluctuations.³³ Therefore, studies highlight a biological model comprising of a combination of decreased serotonin and increased melatonin impacting circadian rhythm in patients suffering from depression with seasonal variation.

Low level of vitamin D due to insufficient exposure to sunlight as observed in countries with severe, prolonged winter is associated with the pathology of various health conditions.³⁴ Broad-spectrum phototherapy, with wavelength between 280-320 nm as obtained from sunlight, enables skin to produce vitamin D from cholesterol.³⁵ In the absence of light wavelength, within the specified range, there is little to none cutaneous synthesis of vitamin D combined with less outdoor activities and also covered clothing that prevent exposure to sunlight on the skin consequently results in low serum levels of vitamin D.³⁵ Also a relationship between depression and serum levels of 25(OH) D has been identified. For example, May et al.³⁶ reported incident depression among very low and low vitamin D groups compared to optimal and normal vitamin D groups after a blood draw in a cohort of individuals with cardiovascular diseases above 50 years. Vitamin D level is reported to be inversely associated with depression.³⁷ Therefore, these factors as described by published studies provide biological evidence implicated in the pathogenesis of low vitamin D level and depression with seasonal pattern. Other associated factors include:

Socio-demographic factors

Population data obtained from 2005 health survey from England indicates that the demographic predictors including older age >65 years, female sex, non-manual socio-economic class, overweight individuals with higher body mass index (BMI >25 Kg/m²), and those with long standing physical illness often exhibit depression associated with low vitamin D level.²⁰ However, in young adult US population (aged 15-39 years), data from the third National Health and Nutrition Examination Survey (NHANES) indicated that women, non-Hispanic blacks, people living below poverty, individuals with higher BMI, persons not consuming supplements, people living in urban areas and in the Southern and Western regions of United States and those with current depression have a higher odds (OR=1.85;p=0.021) of low serum vitamin D ≤50 nmol/L relative to those with serum Vitamin D ≥75 nmol/L.³⁸ One study also indicated that overweight and obese subjects with vitamin D level below 40nmol/L have higher depressive scores on the Beck's Depression Inventory (BDI) compared to those with vitamin D level more than 40 nmol/L.³⁹

Traditionally, sun deprived countries with cold climate that are geographically located in higher Northern latitudes (Canada, North America, Europe) away from equator have been associated with vitamin D deficiency and depression.²⁰ In contrast, some studies have indicated vitamin D insufficiency is observed in a sunny environment from countries including Israel, Saudi Arabia, Florida (USA), Australia, New Zealand, Brazil, India, Lebanon and Jordan.⁴⁰⁻⁴³ Studies from Asian and Middle Eastern countries have reported a high prevalence of vitamin D insufficiency despite a sunny environment that is partly attributed to customary traditional clothing that covers the entire body and poor outdoor activities thus not enabling photosynthesis of vitamin D to occur from melanocytes in the skin.⁴³⁻⁴⁶ Additionally genetic differences, phenotypic skin melanin pigmentation, ability to absorb UVB radiation, cutaneous synthesis of vitamin D are individual demographic differences that contribute to vitamin D insufficiency.⁴⁷ Thus, demographic, genetic, geographic, ethnic, and socio-cultural factors influence vitamin D physiology and metabolism that is associated with physical and mental health.

Clinical correlates

Chronic pain

Vitamin D exerts anatomical, hormonal, neurological and

immunological influences on pain and depression through mediators including neurotransmitters, neuropeptides, hormones and cytokines.⁴⁸ Vitamin D increases serum calcium which is essential for muscle contraction, protein synthesis that affects muscle growth and function.⁴⁹ Consequently, vitamin D deficiency causes musculoskeletal pain, muscle weakness, and myopathy.^{50,51} Low vitamin D level is prevalent in patients⁷ with chronic low back and musculoskeletal pain.⁵²⁻⁵⁵ Among the U.S population, persistent, nonspecific musculoskeletal pain is associated with hypovitaminosis D,⁵⁶ Similarly, in a longitudinal European male ageing study, patients who were pain free at baseline, demonstrated a significant risk of developing new onset chronic widespread pain (CWP) that was significant for those with low vitamin D level.⁵⁷ Women are commonly affected with low vitamin D associated chronic pain condition. For example; one population study reported that low vitamin D concentration associated with CWP is reported in middle aged British women.⁵⁸

Chronic pain patients often suffer from depression that is unresponsive to antidepressant therapy.⁵⁹ Treatment resistance to standard antidepressant therapy in chronic pain patients can be due to low levels of vitamin D as an underlying cause for depression that often goes undiagnosed and untreated. In this context, one randomized, double-blind, placebo-controlled study indicated that vitamin D supplementation in major depressive disorder patients for 8 weeks demonstrated beneficial effects on depression scores compared to the placebo group.⁶⁰ Clinical research studies indicate that low level of vitamin D is associated with chronic pain and comorbid depression.^{61,62} Therefore, early identification of vitamin D deficiency in chronic pain patients with depression not only can have a beneficial therapeutic effect but also prevent disease progression.

Neuropsychiatric condition

Vitamin D is an antioxidant and up-regulates the production of several neurotrophic factors that promote the survival, development and function of neurons.^{63,64} Prior studies have demonstrated that low vitamin D level is associated with white matter abnormalities in the brain including large vessel infarcts,⁶⁵ cerebrovascular accidents,⁶⁶ and fatal stroke in coronary angiography patients.⁶⁷ Vitamin D stimulates phagocytic clearance of β-Amyloid plaques, which is a pathological lesion characteristic of Alzheimer's disease that triggers neuronal degeneration of cerebral cortex.⁶⁸ The exact mechanism by which vitamin D deficiency predisposes an individual to these neuropsychiatric conditions is not clear. Several studies have associated low vitamin D level to increased risk of cerebrovascular pathology and dementia via increased vascular hypertension,⁶⁹ hyperglycemic damage from diabetes,⁷⁰ altered endothelial function, plaque deposition via atherosclerosis,⁷¹ and cerebrovascular diseases.⁷² One longitudinal study indicated that consuming more than 800 IU of vitamin D per day resulted in a five-fold reduction in the risk of Alzheimer's disease after 7 years of follow up.⁷³ Hence, majority of studies highlight that a deficiency of vitamin D is associated with numerous age-related neurological conditions including dementia, cognitive disorders and Alzheimer's disease in older adults.^{73,74}

Vitamin D supplementation not only can prevent neurological disorders such as dementia but also psychiatric conditions including depression.⁷³ Prior studies indicate that low level of vitamin D is associated with the presence and severity of depressive symptoms and thus may pose an underlying biological vulnerability for depression.⁷⁵ A population study conducted among middle to older aged community dwelling European men, reported that lower level of vitamin D is associated with depression.⁷⁶ Similarly, another population based

study conducted in the United States, indicated that low vitamin D levels are associated with depressive symptoms, especially in persons with a history of depression.³⁷ Therefore, among older adults, vitamin D deficiency is not only associated with depressed mood but also cognitive impairment and other comorbidities.^{77,78}

Chronic diseases

Major risk factors for vitamin D deficiency are aging, genetic factors, increased distance from equator, shorter days related to non-summer seasons, indoor lifestyle, darkly pigmented skin, institutionalized/housebound, sunscreens, cover-up clothing, air pollution, smoking, obesity, physical inactivity including chronic diseases (renal disease, liver disease, malabsorption syndromes) and drugs (glucocorticoids, immunosuppressive agents).⁷⁹ Vitamin D deficiency is endemic among people living in Northern latitudes and these individuals are often predisposed to various chronic diseases including hypertension, type 1 diabetes mellitus, autoimmune diseases, multiple sclerosis and chronic depression.⁸⁰ Poor cardiovascular health including systemic hypertension, left ventricular hypertrophy, atherosclerosis, adverse cardiac events, cardio-metabolic conditions including metabolic syndrome and type 2 diabetes mellitus is also associated with low vitamin D level.⁷⁹ In the context of cardiovascular health, the pathophysiology suggested is that vitamin D deficiency up-regulates the renin-angiotensin-aldosterone system and predisposes to arterial hypertension, smooth muscle hypertrophy and chronic heart failure.⁸¹

Two major studies associating low vitamin D level and cardiovascular diseases are well documented. The Whitehall study conducted a 13-year follow up of approximately 5409 older adults and reported that higher concentration of vitamin D was inversely and linearly correlated with both vascular and nonvascular disease mortality and that doubling of serum vitamin D concentration was associated with significant reduction in the mortality rates.⁸² Similarly, the Copenhagen city heart study examined approximately 10,170 Danish adults in 1981-1983 for baseline cardiovascular risk factors and diseases and during a 29 year longitudinal follow up indicated that lower vitamin D level was associated with a 64% higher risk of myocardial infarction, 57% higher risk of premature mortality and 81% higher risk of fatal ischemic heart disease.⁸³ Thus vitamin D deficiency is associated with significant mortality and morbidity from chronic diseases.

Vitamin D deficiency is also commonly observed in older patients with inflammatory bowel disease mostly Crohn's disease and is associated with poor health-related quality of life.⁸⁴ Vitamin D insufficiency and deficiency is prevalent in patients with chronic kidney disease and dialysis patients.^{85,86} Low level of Vitamin D causes an increase in serum parathyroid hormone (PTH) levels causing primary hyperparathyroidism which in turn is associated with symptoms of depressive disorder.⁸⁷ Therefore, studies indicate that low level of vitamin D is associated with chronic diseases and depression.

Musculoskeletal disorders

Musculoskeletal disorders associated with low levels of vitamin D include bone pain, muscle weakness, and low bone mineral density which typically manifests as osteomalacia in adults.⁸⁸ Vitamin D level below 40 nmol/L, is common in North America and predisposes individuals to musculoskeletal disorders, poor bone and muscle health.⁸⁹ One Polish study reported that vitamin D deficiency

is observed in 76.3% of rheumatoid arthritis (RA) and 78.6% of osteoarthritis (OA) patients.⁹⁰ Vitamin D deficiency is associated with adverse health consequences and can exacerbate osteopenia, osteoporosis and fractures in adults.⁹¹

Vitamin D deficiency is also commonly observed in patients with musculoskeletal disorders like fibromyalgia and is frequently associated with depression and anxiety.⁹² Severe vitamin D deficiency leads to osteomalacia and myopathy causing muscle weakness and pain often noted in type 2 diabetic patients with symptomatic relief after vitamin D replacement.⁷⁶ Therefore, early identification and correction of underlying cause such as supplementation of vitamin D and other nutritional deficiency provides a simple resolution of symptoms from musculoskeletal disorders including fibromyalgia and myofascial pain.⁹³

Treatment recommendations

Light therapy

Bright Light Therapy (BLT) also known as phototherapy is considered among the first-line treatments used to replace the diminished sunlight and is administered specifically in the mornings.⁹⁴ Light boxes are available for purchase and emit full spectrum bright light similar in composition to sunlight that exerts effect on chronobiology and autonomic nervous systems of depressed patients.⁹⁴ Light boxes filter out ultraviolet rays and require 20-60 minutes of visual exposure to 10,000 lux of cool-white fluorescent light daily during fall and winter seasons.^{95,96} Bright light is safe with minimal side-effects that include eyestrain, headache, irritability, sleep disturbances and age-related macular degeneration.⁹⁷

Light therapy-induced improvement to corrections of altered circadian rhythm and serotonin neurotransmission during depression with a seasonal pattern is also reported.⁹⁸ Light therapy can be used alone or in conjunction with antidepressants.⁹⁹ Prior studies indicate that when depressed, patients have demonstrated a clinically effective response to bright environmental light and light therapy administered daily for at least several weeks.¹⁰⁰⁻¹⁰² Therefore bright light therapy is an important substitute to sunlight in the management of depression with a seasonal pattern.

Antidepressant treatment

Bupropion (Wellbutrin), a second generation, serotonin reuptake inhibitor, antidepressant, available in an extended release (XR) formulation (150-300 mg/day), has been FDA approved and is effective for the prevention and treatment of depression with a seasonal pattern.¹⁰³ Bupropion is associated with mild side-effects that include headaches, insomnia and nausea.¹⁰⁴ Duloxetine, a serotonin norepinephrine reuptake inhibitor (SNRI) has dual effect as an antidepressant that not only showed a good treatment response in 80% of patients but also maintained a remission rate in 76% of patients after 8 weeks of treatment.¹⁰⁵

Antidepressants, including selective serotonin reuptake inhibitors (SSRIs) such as Fluoxetine (Prozac) and Sertraline (Zoloft) are often used in the treatment of depression with a seasonal pattern.¹⁰⁶ Lamotrigine (mood stabilizer) is used for augmentation of antidepressant medications and is clinically effective after 4-8 weeks of treatment for depression with a seasonal pattern.¹⁰⁷ Augmentation with Modafinil an atypical dopamine inhibitor, is used to reduce fatigue and excessive sleepiness in winter season associated with

the clinical condition.^{108,109} Thus, augmentation agents (Modafinil, Lamotrigine) along with other pharmacological agents (beta blockers, mood stabilizers, tryptophan, cyanocobalamine) are often used in the treatment of depression with a seasonal pattern.¹¹⁰

Melatonin

Melatonin has an agonistic action on MT1/MT2 melatonergic receptors, an antagonistic action at 5HT2c serotonergic receptor and exerts an antidepressant and sleep enhancing effect.¹¹¹ Melatonin and its analogues are available over the counter and is usually administered orally.¹¹² Low dose melatonin is administered in the mornings to regulate the disrupted circadian rhythm associated with winter depression especially in geographical locations where sunlight exposure is minimal and has proven effective in improving depression, sleep disturbances and other health conditions.²⁴

Psychotherapy and Counseling

Cognitive behavioral factors including negative thoughts and a progression from decreased activity enjoyment during fall to a reduced activity frequency during winter is observed especially among women suffering from depression with a seasonal pattern.¹¹³ In one study, six weeks of CBT during two 90 minute group sessions per week was observed to be as effective as 30 minutes of bright light therapy each morning.¹¹⁴ CBT with or without adjunct light therapy is associated with a statistically significant reduction in depression in winter compared to light therapy alone.¹¹⁵

Counselling program regarding dietary approaches targeted towards limiting carbohydrates, increasing physical activity, stress management, increasing social interactions and spending more time in outdoor activities are beneficial.¹¹⁶ Norman Rosenthal, the doctor who first described this condition, indicates that along with psychological counseling, consuming a diet rich in proteins, fruits and vegetables along with other forms of relaxation techniques including Transcendental Meditation (TM), yoga, mindfulness, walking and exercise that alleviates stress and is enjoyable are beneficial. Rosenthal also suggests planning winter vacation to sunny locations can be a preventative strategy. Therefore, CBT and counseling approaches that integrate novel ways of thinking about sad mood and low energy level can provide insight and emotional support to people experiencing depression with a seasonal pattern.

Vitamin D therapy

Patients suffering from recurrent depression with a seasonal pattern have insufficient levels of vitamin D and research investigating this association suggests that daily intake of 100,000 IU of vitamin D may improve the depressive symptoms and general health.¹¹⁷ Vitamin D therapy is available in three treatment modalities that include exposure to sunlight, artificial ultraviolet B (UVB) radiation, and vitamin D3 supplementation.¹¹⁸ Since this condition is prevalent in geographic locations where vitamin D obtained from sunlight is little to none therefore vitamin D3 supplementation is a simple and cost-effective strategy for resolution of depressive symptoms during fall and winter seasons Stewart et al.¹¹⁹ Vitamin D fortification of food is thus recommended not only in cold countries with long winters where sunlight exposure is minimal but also in sunny countries like Asia and Mediterranean regions where some people may not be exposed to sunlight because of full skin covered clothing or an indoor-life Algol et al.⁴⁶ One clinical trial indicated that vitamin D as an adjunctive

therapy to antidepressant (SSRI-fluoxetine) was better than fluoxetine alone in controlling depressive symptoms.¹²⁰ Therefore vitamin D supplementation is used as a preventative and treatment strategy for depression with a seasonal pattern.

Practice Guidelines for Management of Vitamin D Deficiency associated Depression

Prior studies have included practice guidelines.^{1,121-129} These include

- i. Establish a good therapeutic alliance with vitamin D deficient patients with comorbid depression with a seasonal pattern. Such patients can be difficult to treat and a caring, compassionate patient-provider relationship that is trustworthy is the key to successful management.
- ii. Obtain a detailed clinical history, conduct mental status examination, perform thorough physical exam, and formulate a differential diagnosis that is necessary to rule out an organic pathology before associating vitamin D deficiency with psychiatric comorbidities including depression.
- iii. Administer validated screening instruments with excellent psychometric properties (patient health questionnaire (PHQ-9), Beck Depression Inventory (BDI) etc. to assess clinical condition, severity of depressive symptoms and to monitor progress.
- iv. Obtain laboratory exams (CBC with differential, metabolic panel, renal function test, liver function test, serum calcium, phosphorus, parathyroid, alkaline phosphatase, vitamin D level, etc.) and a urine drug screen to rule out substance induced mood disorder. Low vitamin D level may be associated with secondary hyperparathyroidism. Thus, increased serum levels of parathyroid hormone, increased total or bone alkaline phosphatase levels, low 24-hour urine calcium levels, low serum calcium and/or phosphorus level should prompt suspicion for vitamin D deficiency in patients.
- v. Clinical and laboratory exams can be used to rule out causes and risk factors associated with vitamin D deficiency such as renal causes including insufficiency, glomerular filtration rate <60% (decreased 1- α hydroxylase activity), and nephrotic syndrome (decreased levels of vitamin D-binding protein). Gastrointestinal causes such as malabsorption (short bowel syndrome, pancreatitis, inflammatory bowel disease, amyloidosis, celiac sprue, malabsorptive bariatric surgery procedures) and hepatic causes such as severe liver disease or failure (decreased 25-hydroxylase activity) may be associated with vitamin D deficiency and therefore the underlying cause needs to be treated.
- vi. Consider obtaining advanced radiological imaging to visualize underlying anatomic abnormalities or pathological conditions such as decreased bone mineral density (osteopenia or osteoporosis), non-traumatic (fragility) fracture or skeletal pseudo fracture that might suggest possible vitamin D deficiency. Obtain radiologic consultation as deemed necessary. An expert skilled in reviewing these images and placing them in the appropriate clinical context is often the best person to include as part of the treatment team.

- vii. Obtain consultation with psychiatrists, psychologists, internists, radiologists, orthopedics, neurologists, pain management specialists, as part of the multi-disciplinary treatment team when necessary. Establish diagnosis and discuss the treatment plan/ regimen with the patient.
- viii. Pharmacotherapy with multi-target agents (serotonin, norepinephrine, dopamine) like bupropion (NDRI) or duloxetine (SNRI) that act on several neurochemical pathways may be necessary to treat depression with seasonal pattern. Bupropion (Wellbutrin) is considered to be the first-line agent for depression with seasonal pattern. Additionally, if the cause is underlying vitamin D deficiency then vitamin D3 supplementation can be provided along with intake of vitamin D fortified food.
- ix. After initiating pharmacotherapy, monitor for effectiveness, focusing on functional improvements such as sleep, activity, concentration, mood, and even employment status. If the side-effects are intolerable or improvement is not observed, consider increasing the dose or switching to a new class of medication or add adjunct bright light therapy (BLT) in the mornings. In the absence of vitamin D deficiency, BLT is considered the first line therapy for depression with seasonal pattern and antidepressants can be added as an adjunct therapy.
- x. Advise contraception and provide family planning counseling for women of childbearing age as these pharmacologic agents could have teratogenic potential.
- xi. Cognitive behavioral psychotherapy (CBT) when used in combination with pharmacotherapy for depression with a seasonal pattern can be effective and have a better resolution of depressive symptoms.
- xii. Self-management strategies (yoga, mindfulness, self-physical therapy, meditation) complementary and alternative medicine (CAM) modalities (medical massage) are often pooled with mainstream therapies, a practice referred to as integrative medicine. These are proven in sum to be beneficial for the prevention of recurrence or to address treatment-resistant/refractory patients suffering from depression with seasonal pattern.

Conclusion

Low level of vitamin D is associated with depression with a seasonal pattern. It is prevalent in countries far away from the equator with little or no sunshine. However, vitamin D deficiency is also observed in middle-eastern and other countries located in the tropical zone that receive abundant sunshine primarily due to lifestyle factors such as indoor living and wearing fully covered clothing causing lack of exposure of skin to sunlight. Risk factors include advanced age, female gender, pigmented skin, increased body mass index, indoor lifestyle, physical inactivity, sunscreen, covered clothing, geographical location etc. Exact mechanism linking the association between low vitamin D level and depression is not clear. Prior studies have indicated that reduced exposure to sunlight is associated with decreased serotonin activity, an increased production of melatonin by melanocytes in the skin, changes in circadian rhythm, and low vitamin D level in the body. Treatment strategies include light therapy, antidepressant medications, melatonin, psychotherapy/ counseling, and vitamin D therapy. Among all the treatment options, vitamin D

supplementation is a simple, cost effective, efficient preventative and therapeutic strategy for the management of depression with a seasonal pattern associated with vitamin D deficiency.

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Conflict of interest

Author declares there is no conflict of interest in composing this manuscript.

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