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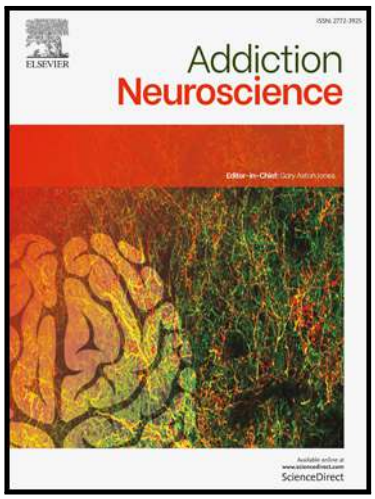

Potential roles for vitamin D in preventing and treating impulse control disorders, behavioral addictions, and substance use disorders: a scoping review

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Potential roles for vitamin D in preventing and treating impulse control disorders, behavioral addictions, and substance use disorders: a scoping review

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Abstract

Vitamin D deficiency is a problem of endemic proportions. Vitamin D is a major regulator of dopaminergic and serotonergic circuits, pathways implicated in addictive disorders. This scoping review (OSF registered as 67yhb) examines preclinical and clinical studies exploring relationships between vitamin D in impulse control disorders, behavioral addictions, and substance use disorders. We searched Ovid MEDLINE, Embase, APA PsycInfo, Cochrane Library, Web of Science, and Scopus databases. We extracted and summarized quantitative and qualitative data through a narrative synthesis and assessed the quality of studies using the Joanna Briggs Institute (JBI) and SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation) criteria. Of 5,442 initial records identified, 28 preclinical and clinical studies were included. For most conditions, we found a negative relationship between vitamin D levels and symptom presence and/or severity. While data suggest a potential beneficial effect of vitamin D on preventing or treating these conditions, there were significant limitations identified by the JBI and SYRCLE assessments. Future studies should include impulse control disorders and other under-explored conditions, address heterogeneity regarding forms, doses, and duration of exposures to vitamin D, and explore vitamin D's potential therapeutic mechanisms.

Keywords

Addictive behaviors; substance use disorders; dopaminergic neurotransmission; vitamin D; impulsive behaviors; compulsive behaviors.

1. Introduction

Vitamin D deficiency is a significant global concern [1], with substantial direct and indirect economic burdens on healthcare systems [2]. Data suggest that vitamin D, vitamin D receptors (VDRs), and VDR polymorphisms contribute to or influence acutely and chronically multiple conditions, including coronary artery disease, musculoskeletal disorders, infectious diseases, cancers, endocrine system dysregulation, inflammatory diseases, autoimmune disorders [3, 4] and psychiatric conditions [5]. Vitamin D contributes importantly to the central nervous system's regulation, development, and function [6-8], affecting specific neurotransmitters and neural pathways.

Vitamin D may influence dopaminergic pathways [9]. Dopamine contributes to pleasurable and rewarding experiences, motivations, and synaptic plasticity [10-12], all of which may influence the development and maintenance of impulse control disorders (ICDs), behavioral addictions (BAs), and substance use disorders (SUDs) [13, 14]. Vitamin D's impact on dopamine may involve the modulation of neuroprotective neurotrophins such as glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3 (NT3), and nerve growth factor (NGF) [15-18]. Vitamin D can also affect dopamine receptors, the expression and activity of dopamine transporters, and multiple enzymes within dopaminergic pathways, including catechol-O-methyl transferase, monoamine oxidase, and tyrosine hydroxylase [19, 20]. Vitamin D may also protect dopaminergic neurons by preventing oxidative damage through balancing agents such as glutathione and glutamate [21, 22] and inhibiting nitric oxide synthase [23]. The absence of VDR signaling may promote downregulation of dopaminergic signaling [20, 24-27].

Dopaminergic alterations may reduce brain serotonin levels, which, along with dopaminergic changes, may promote deficits in inhibitory control [28]. Furthermore, serotonergic regulation has been linked to vitamin D levels. Mechanistic underpinnings include vitamin D regulation of tryptophan hydroxylase, the

rate-limiting enzyme of serotonin synthesis [24, 29, 30]. Serotonin also contributes to long-term synaptic plasticity [31]. Given that serotonin has been implicated in brain processes linked to pleasure [32], motivation [33], and reinforcement [34], it, along with dopamine, may impact behavior-organizing and reward-related brain circuits underlying impulse control, substance use, and addictive behaviors [35].

Vitamin D also may impact GABA, whose signaling contributes to behavioral and psychological manifestations of addictions [36]. GABA has been linked to multiple aspects of SUDs, including severity, craving, withdrawal, relapses [37-40], and impulse control [41]. Both neurotrophic factors (i.e., brain-derived neurotrophic factor (BDNF)) [42] and dopamine synthesis associated with vitamin D levels [43] may influence GABA release [44]. Thus, vitamin D may operate through GABA to impact impulse control, reward, and motivation processing [11, 45].

In summary, vitamin D is linked to the functioning of several key neurotransmitters implicated in impulsivity, reward-seeking, and other features associated with addictions. Insufficient vitamin D levels may influence these neurotransmitter systems, warranting further examination regarding how vitamin D may help prevent or treat addictions.

ICDs involve failures to resist impulses, temptations, or drives to perform behaviors harmful to the person or others. According to the DSM-5, ICDs also are characterized by elements of diminished consideration of social norms or the rights of others. DSM-5 ICDs include oppositional defiant disorder, intermittent explosive disorder, conduct disorder, kleptomania, and pyromania [46]. SUDs are also characterized by impulsivity [47-52]. SUDs constitute a growing public health concern worldwide. Approximately 20.4 million people in the United States were diagnosed with SUDs in 2019 [53]. Elevated prevalence estimates of vitamin D deficiency have been reported in individuals with SUDs [25]. As Vitamin D may target systems implicated in SUDs [15, 54-58], its use in preventing and treating SUDs should be examined further.

Like SUDs and ICDs, BAs are often characterized by elevated impulsivity [59]. Although DSM-5 BAs include gambling disorder and research criteria for internet gaming disorder [60, 61], a broader range of conditions may constitute BAs. Such BAs may involve compulsive tanning, internet use, screen media activity, food consumption, shopping/buying, sexual behaviors, and others [25, 62-67]. Serotonin and dopamine may contribute to BAs as well as SUDs and therefore relate to vitamin D levels as described above [64, 68], albeit with certain caveats [69-71].

To our knowledge, no other reviews have explored data on the relationships between vitamin D and all these DSM-5 conditions (i.e., ICDs, BAs, and SUDs). Although research on vitamin D's role in regulating neurotransmitters and influencing neurocircuits is growing [72], preclinical and clinical studies on its effects on brain function and behavior remain limited. Current gaps in the field include understanding the underlying mechanisms by which vitamin D could have preventive or therapeutic effects on these conditions, whether vitamin D deficiency is prevalent in these disorders, and whether vitamin D deficiency or vitamin D supplementation influence clinical outcomes [9, 25, 72-76]. The awareness of these uncertainties, coupled with knowledge about easy access to and low cost of vitamin D supplements, motivates the current scoping review.

2. Material and methods

This scoping review is informed by the framework described by the Joanna Briggs Institute (JBI) [77] and is being reported in accordance with the PRISMA Extension for Scoping Reviews (PRISMA-ScR) [78]. The protocol for this review was registered on the Open Science Framework (OSF) in December 2022 (https://osf.io/ea6vr) [79].

2.1. Search strategy

An experienced medical librarian (MCF) analyzed the medical subject heading (MeSH) [mesh.med.yale.edu] of known key articles provided by the research team and performed scoping searches in each database. An iterative process was used to translate and refine the searches between databases. To maximize sensitivity, the formal search used controlled vocabulary terms and synonymous free-text words to capture the concepts of "vitamin D" and "addiction." Using the PRESS standard [80], the search strategy was then peer-reviewed by a second librarian not otherwise associated with the project. The authors then checked for additional relevant articles by analyzing the references and citing references from included studies.

A search was done on December 14, 2022, and updated on March 22, 2023, and October 3, 2023. The comprehensive search included multiple databases: Ovid MEDLINE, Embase (Ovid), APA PsycInfo (Ovid), Cochrane Library, Web of Science (Core Collection), and Scopus. No language or date limits were applied. The search results included published peer-reviewed articles and gray literature. Tables A.1 to A.6 of Appendix A of supplementary materials provide the search strategies for all databases.

The final search results were pooled in EndNote 20 (endnote.com), and duplicates were removed by the Reference Deduplicator (library.medicine.yale.edu/reference-deduplicator). This set was uploaded to Covidence (covidence.org) for screening. Through a two-stage collaborative review process, all identified articles were screened independently by at least two reviewers (authors LJK, BBY, and RK).

2.2. Article selection

This scoping review considered both preclinical and clinical studies. Eligible experimental and quasi-experimental study designs included randomized controlled trials (RCTs), non-randomized controlled trials (NRCTs), before-and-after studies, and interrupted time-series studies. In addition, analytical observational studies, including prospective and retrospective cohort studies, case-controls and analytical cross-sectional studies, descriptive observational study designs, case series with a sample size of more than two participants, and descriptive cross-sectional studies were also considered for inclusion. Systematic reviews and meta-analyses were excluded.

Inclusion criteria were studies reporting on putative neurobiological mechanisms through which vitamin D may influence ICDs, BAs, and SUDs; studies investigating vitamin D levels, and preclinical or clinical outcomes related to the conditions mentioned earlier; and exposure to vitamin D and preclinical or clinical outcomes related to these conditions.

The co-authors applied the eligibility criteria during the initial title and abstract review. Disagreements were resolved through discussions with the senior author (GAA) until a consensus was reached. The co-authors then applied eligibility criteria through selected papers based on a full manuscript review. If

studies were not retrievable, we contacted the authors of these studies. Studies retrieved at this stage were included in the screening process.

2.3. Data extraction, synthesis, and quality assessment

The authors LJK, RK, and BBY conducted the data extraction process. The following general characteristics were extracted from each study: publication author and year, study design, objectives, description of the target population, context, and results. We summarized the extracted data quantitatively (when applicable) and qualitatively through a narrative synthesis. We did not perform any statistical analyses.

A scoping review does not mandate a critical appraisal. Due to this reason, the registered OSF protocol did not list steps pertaining to the qualitative assessments of the included manuscripts. However, there is also research suggesting that assessing the quality of evidence is a valuable aspect of this type of review [81]. Therefore, quality assessment of each manuscript was added to this review. We selected the critical appraisal tools provided by the JBI System for the Unified Management of the Assessment and Review of Information (JBISUMARI) to evaluate cohorts, case-control studies, cross-sectional studies, and RCTs [82, 83]. For preclinical studies, we chose the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE's) risk of bias tool [84]. The articles included were assessed independently by two co-authors (LJK, BBY, AB, and RK). Conflicts were resolved through discussions until a consensus was reached.

3. Theory

There are multiple areas of overlap between vitamin D, ICDs, BAs, and SUDs preclinically and clinically, in terms of mechanisms of action (i.e., modulation of dopamine synthesis and behavior-organizing and rewarding brain circuits) and longitudinal trajectories between vitamin D deficiency and the development, progression, and maintenance of conditions (i.e., exposure to vitamin D as being associated with changes in drug sensitivity and reduction in the symptomatology of SUDs). Although this level of overlap in which sufficient levels of vitamin D may have a preventive/therapeutic role is promising, multiple unanswered questions remain, such as the degree to which the current literature supports cause-effect relationships and which forms and doses of vitamin D may constitute effective interventions.

4. Results

Of the 19,723 initial studies in the primary search database, 14,281 duplicates were identified by Reference Deduplicator, Covidence, or manual processing. Of the 5,442 records screened for title and abstract relevance, 5,312 were excluded, and 125 retrievable studies were assessed for full-text eligibility. 28 studies were included for data extraction. A PRISMA diagram of the search process is shown in Figure 1.

Of the 28 studies, one preclinical study evaluated BAs, and 27 evaluated SUDs. Among the 27 SUD-related studies, eight were preclinical, Among the eighteen clinical studies, five were cross-sectional, one was a case-control, six were cohort, and six were RCT. One study involved both preclinical and clinical aspects. The clinical part included case-control and cross-sectional designs. We assessed each part separately in the qualitative evaluations. The study details are summarized in Table 1.

Our assessments of the quality of the literature, using the JBI and SYRCLE's criteria, are summarized in Tables B.1 to B.5 of Appendix B of supplementary materials.

We could not extract some methodological details for the preclinical studies, particularly in the selection bias, performance bias, detection bias, and attrition bias domains. More details were needed regarding random group assignments, random housing, blinding of study staff, and possible differences between animal groups.

Of the 19 studies with clinical components assessed by JBI, there were only six RCTs; the remainder were observational. Two of the six cross-sectional studies did not state how confounding factors were addressed. Of the two case-control studies, only one stated a strategy for addressing confounding factors. In the other case-control study, it was unclear whether the groups were comparable and whether the criteria to identify cases and controls were the same. Half of the six cohort studies needed to be made clearer about strategies employed to address incomplete follow-up. In one cohort study, it was unclear how they approached confounding factors, while another did not elaborate on the confounding factors. Two of the other cohort studies contained participants who, at baseline, already had the outcome of interest. Two of the six RCTs did not address whether those who delivered the treatments or assessed outcomes were blinded to treatment assignments. In two of the RCTs, participant follow-up was incomplete, and the differences in follow-up between groups were not described and analyzed adequately. Between-group follow-up was unclear on another RCT.

4.1. Vitamin D, ICDs, and BAs

Our search results did not reveal studies on vitamin D's association with ICDs as defined in the DSM-5. One preclinical study investigated gambling disorder.

4.1.1. Gambling disorder

The rat gambling task, adapted from the Iowa gambling task (IGT) in humans, evaluates decision-making in the context of variable wins and losses and uncertain outcomes [85]. One preclinical study examining task performance in rats with developmental vitamin D deficiency showed some alterations in performance and training compared to controls. However, no significant impairments in decision-making processes were observed in rats with acquired vitamin D deficiency [86].

Overall, ICDs' relationship with vitamin D has not been examined, while there was only one negative preclinical study on gambling disorder.

4.2. Vitamin D and SUDs

We appraised manuscripts on six substance-related conditions (alcohol, opioids, cannabis, tobacco, stimulants, and benzodiazepines) in which vitamin D was studied within their context using preclinical and clinical approaches. Five studies considered alcohol, fifteen opioids, and six stimulants. Two studies considered tobacco, and one each considered cannabis and benzodiazepines.

4.2.1. Alcohol

All five alcohol-related studies investigating vitamin D were clinical, including two cross-sectional [87, 88], one case-control [89], one cohort [90], and one RCT [91].

A cross-sectional study of 174 Nepalese inpatients with alcohol use disorder (AUD, established through DSM-IV criteria) at eight alcohol/drug treatment centers found that vitamin D deficiency (serum 25[OH]D levels ≤20 ng/mL) was observed among 64% of patients. The Alcohol Use Disorder Identification Test (AUDIT) was administered to assess the severity of alcohol use. A t-test comparison of mean vitamin D levels revealed significantly lower levels in participants who felt guilt about drinking, used alcohol as an eye-opener, had histories of relapse after alcohol treatment, and were categorized as alcohol dependent based on AUDIT criteria compared to individuals without these features. Other AUDIT items such as frequency of alcohol use and alcohol consumed per drinking episode were not significantly correlated with vitamin D levels. The study found no significant correlation between vitamin D status and other SUD measures including number of reported alcohol withdrawal symptoms [88].

These findings contrast with another cross-sectional study in Korea with a sample size of 7,010 individuals. Based on a self-report questionnaire designed by the Korea Centers for Disease Control and Prevention [92], male subjects with adequate levels of vitamin D (serum 25(OH)D levels ≥ 30 ng/mL) reported more frequent drinking, more alcoholic beverages consumed, and higher average daily alcohol intake compared to males with low levels of vitamin D (serum 25(OH)D levels < 30 ng/mL). These findings persisted after controlling for age, smoking status, physical activity, liver function, and dietary intake. However, similar correlations were not observed in female subjects [87].

One case-control study showed that the single nucleotide polymorphism of the VDR gene *FokI* was associated with impulsivity in males with AUD. DNA samples from 148 individuals with AUD revealed that male participants with a CC genotype of *FokI* scored highest on global and attentional impulsivity on the BIS-11 [93]. This allelic variant of the VDR gene was not associated with impulsivity in females with AUD [89].

A cohort study considering AUD severity and craving in 47 patients with AUD undergoing inpatient detoxification treatment did not reveal an association between vitamin D levels and alcohol craving based on the self-reported Obsessive Compulsive Drinking Scale [94]. This study also used the Alcohol Dependence Scale high-risk sample to assess AUD severity and categorize individuals as having heavy drinking or not [95]. No associations with vitamin D levels were observed [90].

Only one RCT explored the association between treatment with vitamin D and calcium or placebo in people with AUD. Fifty-five individuals undergoing inpatient alcohol withdrawal treatment for two weeks were given a daily dose of calcium carbonate (800 mg) combined with a small amount of vitamin D (5 μg) and were compared to a group receiving sodium bicarbonate (1,000 mg). Reduced alcohol craving intensity (assessed with the Obsessive Compulsive Drinking Scale) and faster attenuation of withdrawal symptoms (assessed with the Clinical Institute Withdrawal Assessment Scale for Alcohol) [96] were observed through the first week of abstinence in the group receiving calcium carbonate and vitamin D, compared to the group receiving sodium bicarbonate [91].

4.2.2. Opioids

Fifteen studies considered opioid use relative to vitamin D. Eleven were clinical, including three cross-sectional studies [97-99], five cohorts [100-104], and three RCTs [105-107]. The remaining four studies were preclinical [25, 108-110].

Kemény et al. investigated several aspects of vitamin D's effects on opioid use in preclinical settings. First, they tested morphine effects using multiple models of conditioned place preference (CPP). They compared vitamin-D-deficient mice (fed a vitamin D-deprived diet for eight weeks) and knockout-VDR mice to vitamin-D-sufficient mice. While all groups developed strong morphine-induced CPP responses to the highest morphine dose tested (20 mg/kg), only the vitamin-D-deficient and VDR-knockout mice developed strong CPP responses at lower doses. These results suggest that deficiencies in VDR signaling may increase sensitivity to the rewarding effects of opioids. After restoring vitamin D deficiency to normal levels, the replenished mice developed a CPP pattern similar to the vitamin-D-sufficient mice, highlighting the potentially reversible nature of vitamin D deficiency effects on opioid use. However, in terms of prevention opportunities, the administration of calcitriol to vitamin-D-sufficient or wild-type VDR mice did not prevent the development of CPP for morphine [25].

Basal pain threshold and analgesic effects of opioids relative to vitamin D were evaluated using a hot plate test. In this experiment, mice were placed on a 52°C hot plate, and withdrawal response time (jumping to escape the harmful stimulant and paw licking to alleviate the effects of the thermal stimulus) was measured [111]. Both knockout-VDR and vitamin-D-deficient mice demonstrated higher basal thermal nociceptive thresholds and greater opioid analgesia effects compared to mice with wild-type VDR and mice with sufficient vitamin D levels. This effect was reversed once mice received oral vitamin D replenishment [25]. Repeated exposure to opioids in these vitamin-D-deficient mice also resulted in a faster opioid tolerance development, measured by the number of days needed to reach tolerance with daily morphine injections [25].

Regarding the chronology and magnitude of opioid withdrawal symptoms, vitamin-D-deficient mice and knockout-VDR mice showed earlier signs of withdrawal manifestation and more significant severity of withdrawal symptoms, suggesting greater morphine dependence. These symptoms included behaviors such as shakes, tremors, paw-licking and paw-chewing, acute weight loss, and diarrhea measured within 25 minutes of opioid-antagonist injection (naloxone). These behaviors were alleviated once vitamin-D-deficient mice were fed vitamin-D-sufficient diets [25].

Another preclinical study [108] using an earlier version of the hot plate test [112] reported that vitamin-D-deficient rats had elevated basal pain thresholds and responses to morphine's analgesic effects. Also, vitamin D hastened the development of tolerance to morphine. Pretreatment with cholecalciferol (1000 IU./Kg/day for five days) brought the basal pain threshold back to normal in the vitamin D-deficient rats and decreased responsiveness to the analgesic effects of morphine [108]. In another study, 36 rats were divided into six groups: saline, morphine, morphine plus almond oil, and morphine plus 250, 500, and 1000 IU/kg of vitamin. Then, rats were tested for CPP and locomotor activity using an open-field apparatus. This study, contrary to Kemény et al., showed that paired morphine with vitamin D, and in particular, higher doses of vitamin D, enhanced morphine-induced CPP without changing locomotor activity in the open-field test [109].

Interestingly, the same group measured how vitamin D altered oxidation/anti-oxidation profiles (via measuring malondialdehyde, catalase, superoxide dismutase, total antioxidant capacity, thiol, and nitric oxide) by collecting cortical and hippocampal brain regions from the rats for biochemical assessments and molecular quantification. They showed that rats receiving morphine and treated with high doses of vitamin D (500-1000 IU/kg) developed an overall improved antioxidant profile (higher catalase and

superoxide dismutase activity and total antioxidant capacity) and attenuated oxidation profile (decreased malondialdehyde levels) when compared to rats receiving only morphine [109].

Another preclinical study using CPP divided 80 male rats into two main groups that either received saline or morphine (5 mg/kg, intraperitoneally). These groups were further subdivided into subgroups receiving intraperitoneal vitamin D vehicle (placebo), 5 μg/kg of vitamin D, or 10 μg/kg of vitamin D. Administration of vitamin D at a dosage of 10 μg/kg before the CPP conditioning phase significantly reduced the time spent in CPP model morphine chambers. Furthermore, receiving vitamin D at dosages of 5 or 10 μg/kg before or after conditioning notably reduced morphine-seeking behavior compared to placebo [110].

A clinical-focused study analyzing data from the National Health and Nutrition Examination Survey (NHANES, 2003–2004) [113] concluded that subjects with deficient (<12 ng/ml) or insufficient (12 to 20 ng/ml) levels of vitamin D were more likely to use opioid-based analgesics compared to subjects with sufficient serum vitamin D (>20 ng/ml). This pattern remained statistically significant when data were also adjusted for age, sex, history of fractures, season of blood draw, and presence of chronic pain. Among 163,531 primary care patients at Massachusetts General Hospital evaluated between 2014–2016, the presence of vitamin D deficiency and insufficiency in individuals with opioid use disorder (OUD; n=2,772) was significantly higher compared to matched (by age, sex, race, and primary care provider) control cases without OUD (n=8,265) [25].

A cross-sectional study conducted in a 3-week outpatient pain rehabilitation program observed differences in opioid dosages used and durations of opioid use in vitamin-D-deficient patients (serum 25[OH]D levels ≤20 ng/ml) compared to vitamin-D-sufficient patients. The average daily morphine equivalent dose was 133.5 mg for vitamin-D-deficient patients, while those with sufficient levels of vitamin D had an average dose of 70.0 mg. Patients deficient in vitamin D also had a longer mean duration of opioid use of 71.1 months, compared to 43.8 months for those with sufficient levels of vitamin D [98].

A cross-sectional study of 500 patients undergoing methadone maintenance treatment (MMT) demonstrated that lower levels of vitamin D were correlated with higher depression and anxiety scores measured using the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI), respectively [114, 115]. Higher dosages of methadone and longer durations of MMT were observed with lower levels of vitamin D; however, these correlations were not statistically significant [97].

Another cross-sectional study of 185 patients with morbid obesity undergoing laparoscopic bariatric surgery demonstrated no significant difference between patients with sufficient or deficient levels of vitamin D (serum 25[OH]D levels ≤20 ng/ml) in post-operative pain scores or total opioid consumption. This correlation remained insignificant when adjusting for age, sex, body mass index, smoking status, diabetes mellitus, chronic pain syndrome, and chronic usage of steroids and opioids [99].

A prospective cohort of 100 palliative cancer patients showed that patients with lower serum levels of vitamin D (≤20 ng/ml) had higher requirements for fentanyl, a powerful synthetic opioid. The correlation remained significant when adjusting for disease severity but not when adjusting for age [101].

Another prospective cohort in a colorectal cancer population classified 112 Chinese patients before surgery as vitamin-D-deficient and vitamin-D-sufficient using a serum cutoff point of 20 ng/ml.

Preoperatively, all measured baseline pain indexes showed significant differences between the two groups. Patients with vitamin D deficiency started experiencing pain earlier than patients with normal levels, and their pain endurance threshold was lower. During the operation, patients with vitamin D deficiency had higher consumption of sufentanil (a synthetic opioid), but no differences in consumption of remifentanil (another synthetic opioid), compared to vitamin-D-sufficient patients.

In the post-operative course of the colorectal cancer patients, patient-reported Visual Analog Scale (VAS) scores were collected by the anesthesia nurse at 6 hours, 12 hours, 24 hours, and 48 hours. The VAS is a subjective assessment tool in which participants self-report their pain level along a 10-centimeter line spanning from "no pain" to "worst pain" [116]. Patients with vitamin D deficiency reported higher pain scores at 6 hours, 12 hours, and 48 hours compared to vitamin-D-sufficient patients. Moreover, vitamin D deficiency was associated with considerably higher use of fentanyl for pain through patient-controlled analgesia (PCA) during the first 24 hours after the operation [104].

A large retrospective cohort study [102] identified an initial 11,751 study subjects undergoing common surgical procedures, as chosen by prior cohorts focusing on chronic opioid use [117]. Among a subgroup of 5446 participants without pre-surgery opioid use for at least six months and with at least two months follow-up receiving post-surgery opioid-based pain relief, patients with vitamin D deficiency (< 12 ng/mL), in comparison to those with vitamin D sufficiency (≥ 20 ng/mL), but not a vitamin-D-insufficient group (12 to 20 ng/mL), had a higher average number of days (mean of 1.7 more days of opioid use per year) and dose of using opioids (an additional 98.7 milligrams of morphine equivalent doses per year) in multivariable analyses. Among the 11,713 subjects who did not have a history of OUD, those with deficient 25(OH)D levels had increased severity of OUD during the follow-up period when compared to those with sufficient 25(OH)D levels [118]. This outcome also differed between the groups with insufficient (12 to 20 ng/mL) versus sufficient levels of vitamin D [102].

One cohort study of people with OUD suggested that elevated vitamin D levels may increase retention in MMT and improve outcomes based on two observations. First, among patients who had available baseline vitamin D upon starting MMT treatment, higher vitamin D levels correlated with longer cumulative retention in treatment compared to those with lower vitamin D levels. Second, a tendency towards shorter cumulative treatment retention was observed in individuals with vitamin D deficiency (defined as <20 ng/mL) while undergoing treatment. With patients' improving vitamin D levels over time, there was a positive linear correlation with weight gain rates, suggesting a healthier status [103].

Another prospective longitudinal cohort was conducted in outpatient opioid agonist therapy (OAT) clinics in Western Norway. Participants were prescribed either buprenorphine-based medications or methadone. Six-hundred-and-sixty-six participants had baseline assessments of vitamin D levels, with deficiency defined as serum 25(OH)D level <20 ng/mL and severe deficiency as <10 ng/mL. Among participants, the dose of opioid agonist prescribed, and the use of non-OAT opioids were not associated with vitamin D levels [100].

One RCT used 50,000 IU of vitamin D every two weeks for 12 weeks and measured inflammatory cytokine levels, insulin expression, and withdrawal symptoms. The clinical opiate withdrawal scale [119] evaluated withdrawal signs and symptoms at baseline and after 3-months of treatment. While vitamin D levels improved by the end of the trial in the group receiving the vitamin D intervention vs placebo, changes in withdrawal symptoms between the two groups were not statistically significant. Associations were observed between an overall reduction in systematic inflammation and vitamin D treatment,

inflammatory cytokines, and metabolism-related genes. Ameliorated metabolism regulation was reported with respect to the potential adverse effects of MMT [106].

Another RCT used the same vitamin D supplement intervention in patients receiving MMT. Vitamin D supplementation significantly affected various metabolic outcomes, including decreased fasting plasma glucose levels, insulin levels, and total cholesterol levels. Moreover, as assessed using the Pittsburgh Sleep Quality Index, the supplementation was linked to better sleep quality, including subjective sleep quality, sleep latency, and sleep duration, among other measures [120]). Patients receiving vitamin D also had improvements in depression and anxiety on the BDI and BAI, respectively, during the three-month intervention [105].

One RCT conducted by the same group administered 50,000 IU vitamin D supplements or placebo every two weeks for 24 weeks in subjects receiving MMT and found positive effects on BDI scores, as well as some measures of cognitive functioning, but no significant improvements in BAI scores, when compared to the MMT patients who received placebo [107]. They also evaluated performance on the IGT, which assesses decision-making and learning through card selection involving wins and losses [121]. IGT performance significantly improved in subjects treated with vitamin D in comparison to subjects receiving placebo [107].

4.2.3 Cannabis

We found one preclinical study discussing cannabis use relative to vitamin D [122]. Cannabis use was discussed as a co-occurring substance with opioid use in another study [100].

Altered sensitivity to acute cannabis administration in vitamin-D-deficient rats was investigated using memory and information-processing tests. Working memory parameters were evaluated using a delayed matching to sample (DMTS) task, which consists of subjects initially trained to identify a sample stimulus from other introduced comparison stimuli. Variable delays between the presentation of the sample stimulus and the introduction of the comparison stimuli are tested, leading to an understanding of the rat's ability to hold and maintain information in their working memory for different lengths of time [123, 124]. The administration of Δ9-tetrahydrocannabinol (THC) at several doses (0, 0.3, 0.6, 1.25, 2.5 mg/kg) 15 minutes before performing DMTS (with variable delays of 0–24 s) resulted in negative dose-dependent performance on the DMTS task at all delay points in both control and vitamin-D-deficient rats. In the other component of the experiment, the authors examined pre-pulse inhibition (PPI). Traditionally, PPI measures the capacity of a weak initial stimulation (pre-pulse) to suppress the startle response from a subsequent stronger startle stimulus (pulse). They found that vitamin-D-deficient rats showed enhanced PPI after acute THC administration, and this was not observed in the control group, together suggesting that vitamin D deficiency may enhance sensitivity to the acute effects of THC on PPI [122].

Only one cohort study (detailed in section 4.2.2 [100]) explored cannabis use in patients clinically, and these individuals received OAT in outpatient settings. Lower baseline vitamin D levels were associated with more frequent consumption of cannabis [100].

4.2.4. Tobacco

We found one preclinical study examining the relationship between nicotine and vitamin D [25] and one RCT considering tobacco use relative to vitamin D [125].

Preclinically, a stronger CPP for nicotine was observed in VDR-knockout versus wild-type mice, a finding suggesting enhanced rewarding effects of nicotine with vitamin D deficiency. Considering preclinical studies suggesting an influence of age on susceptibility to the rewarding effects of nicotine [126], studies were conducted with mice younger and older than eight months. These experiments showed that an association between VDR knockout and higher CPP only in mice younger than eight months [25].

The only clinical study assessing the effects of vitamin D supplementation in people who smoke tobacco was a double-blinded, placebo-controlled RCT. Subjects from an outpatient clinic received 50,000 IU vitamin D supplement or placebo every two weeks for 24 weeks. No significant effects of vitamin D administration were observed on nicotine use, based on the Nicotine Dependence Syndrome Scale [127]. However, receiving vitamin D improved secondary outcomes such as BDI scores and some metabolic profiles, including decreases in levels of fasting plasma glucose and insulin and increases in total antioxidant capacity and glutathione levels [125].

4.2.5. Stimulants

Six studies considered stimulant use relative to vitamin D. The studies included four preclinical [27, 29, 128, 129], one cohort [100], and one RCT [130].

One preclinical study [29] tested the effects of acute single-dose calcitriol administration (10 µg/kg, intraperitoneal) vs. vehicle on several outcomes: tonic and phasic dopamine release after an acute single administration of amphetamine (2.5 mg/kg, intraperitoneal) and drug-seeking behaviors. Using micro-dialysis and fast-scan voltammetry recording, calcitriol versus placebo increased tonic and phasic dopamine release. Based on quantification of "licking" to obtain amphetamine, mice fed with vitamin-D-deficient diets had higher cumulative amphetamine consumption than mice fed with vitamin-D-sufficient diets, and pre-treatment with calcitriol vs. placebo decreased licking for amphetamine without altering total fluid intake. Vitamin-D-deficient vs. vitamin-D-sufficient diets were linked to more amphetamine-seeking behaviors [29].

Another study administered a single dose of amphetamine (0, 0.6, 1.25, and 2.5 mg/kg) to male and female rats fed with vitamin-D-deficient and vitamin-D-sufficient diets and evaluated amphetamine-induced locomotor activity. Vitamin-D-deficient adult female rats exhibited heightened responsiveness after receiving 2.5 mg/kg of amphetamine when compared to control females. This locomotor activity difference was not evident in vitamin-D-deficient adult male or juvenile rats compared to controls [27].

Another preclinical study examined potential neuroprotective effects of vitamin D on methamphetamine-induced neuronal toxicity. Male Fischer-344 rats received daily placebo or calcitriol (1µg/kg, subcutaneous) administration for eight days. After the seventh day of treatment, the rats were challenged with either 5 mg/kg subcutaneous methamphetamine or saline administered four times at 2-hour intervals on the day, resulting in a cumulative dose of 20 mg/kg for the day. Then, a week later, the striata and nuclei accumbens were collected from the animals to conduct high-performance-liquid-chromatography analysis on monoamines and their metabolites. In animals subjected to both calcitriol and methamphetamine, there was less methamphetamine-induced depletion of dopamine, serotonin, and their metabolites in comparison to vehicle-treated animals [128].

Using a similar exposure to calcitriol and methamphetamine as previously [128] except using a wider range of calcitriol doses (0.3, 1.0, or 3.0 µg/kg doses), investigators tested whether calcitriol influenced

potassium- and d-amphetamine-evoked overflow of serotonin and its primary metabolite 5-hydroxyindole acetic acid [129]. Rats pre-treated with vehicle had more significant deficits in measured potassium- and d-amphetamine-evoked overflow of serotonin vs. the group pre-treated with calcitriol, suggesting calcitriol has protective effects against methamphetamine-induced serotonin depletion [129].

One clinical cohort manuscript considered co-occurring substance use in patients receiving OAT (see section 4.2.2). No significant associations were observed between baseline serum 25(OH)D levels and frequency of stimulant use [100].

One RCT assessed vitamin D supplementation (cholecalciferol) in people who used amphetamines and used the brief psychiatric rating scale (BPRS) as the outcome [130]. The BPRS measures multiple symptoms related to depression, anxiety, hallucinations, psychosis, and unusual behavior [131]. Forty days of daily administration of 1000IU cholecalciferol (versus placebo) led to more improvements in BPRS scores [130].

4.2.6. Benzodiazepines

Only one cohort study (described in section 4.2.2) considered benzodiazepine use relative to vitamin D. In the study, there were no associations between baseline and longitudinal measurements of serum vitamin D levels and frequency of benzodiazepines consumption [100].

Overall, a significant proportion of the studies showed that lower vitamin D levels were linked to higher sensitivity to and consumption of substances, more severe withdrawal, and poorer secondary outcomes.

5. Discussion

Here, we reviewed the existing literature on vitamin D's potential preventive and therapeutic role in ICDs, BAs, and SUDs. We chose to include these conditions in one review due to vitamin D's shared effect on addiction-related pathways and brain circuits, which overlap among various behaviors and substances [9, 35, 37, 41, 48, 132-134].

Impulsivity is a core component of addictive patterns consisting of risk-taking and impaired action inhibition [132, 135]. Our search did not reveal studies on the association between vitamin D and DSM-5 ICDs. However, vitamin D deficiency is associated with higher impulsivity in preclinical [136, 137] and clinical settings [66, 73], perhaps due to its influence on serotonergic and dopaminergic systems [9, 138, 139]. There were also a few studies on other conditions with impulsive components that were categorized as ICDs in earlier versions of the DSM. Case reports of people with trichotillomania have suggested improvements through vitamin D supplementation [62, 140]. Individuals with binge eating disorder and vitamin D deficiency also demonstrated poor performance in impulsivity-measuring tasks [73].

Among BAs, vitamin D did not alter gambling task outcomes in preclinical settings. An improvement in IGT performance was observed among subjects undergoing MMT who received vitamin D injections [107]. One condition of note with features consistent with BAs is compulsive tanning [141]. One of Kemény et al.'s experiments suggested increased sensitivity to the rewarding effects of ultraviolet radiation (UVR) in the absence of vitamin D in preclinical settings. Correcting vitamin D levels restored normal sensitivity to UVR and reversed this behavior [25].

There is a noticeable gap in literature exploring gambling disorders relative to vitamin D in clinical settings and certain other BAs or related conditions (gaming disorder, compulsive tanning, internet addiction, problematic use of social media, compulsive buying/shopping, and others).

Vitamin D's impact on SUDs, specifically alcohol and opioids, has been examined more thoroughly. In addition, possible pathways and mechanisms at a molecular level are also better understood in SUDs.

Alcohol use is linked with vitamin D deficiency and malnutrition [142], but cause-and-effect relationships are not established [143]. Multiple studies suggest promising impacts of vitamin D and multiple AUD outcomes such as withdrawal symptoms, craving, relapse, abstinence duration, and AUD severity [87, 88, 90, 91]. One study suggested no relationship between vitamin D and craving and heavy drinking [91]. However, it should be noted that this study's JBI quality assessment score was low. Regarding relationships between vitamin D and alcohol use, potential contributing factors may involve an impact of vitamin D on calcium homeostasis, alcohol-induced liver damage and subsequent hepatic vitamin D metabolism, physical activity, nutrient intake, sun exposure, and different VDR gene polymorphisms [89, 144-147]. Therefore, associations between vitamin D and AUD may involve other additional factors.

Of substances, opioids have been arguably the most well-studied in preclinical and clinical studies of vitamin D. Based primarily on preclinical studies, vitamin D deficiency has been linked to increased sensitivity to opioids and their analgesic effects, hastened the development of tolerance, and earlier and more severe withdrawal [25, 108, 110]. In contrast, one study showed potentiated CPP response following vitamin D injection. However, the study also suggested overall vitamin-D-related improvements in oxidation/anti-oxidation profiles [109].

Multiple observational studies have linked lower levels of vitamin D and higher opioid dosages and durations of use in both groups with and without OUD [25, 98, 101-104]. Furthermore, lower vitamin D levels were associated with higher depression and anxiety scores, poorer sleep quality, shorter cumulative retention in MMT, greater release of inflammatory cytokines, and metabolism dysregulation among people with OUD [97, 98, 103, 105-107]. However, some studies did not replicate these findings [99, 100]. Importantly, suggested beneficial effects have been noted across a wide range of vitamin D doses and durations of exposure. Therefore, while vitamin D's role as an adjuvant preventive or therapeutic intervention for OUD seems promising, further investigation is warranted regarding dosing and administration.

While there is considerably less research on tobacco than opioids, available data suggest that vitamin D levels are lower in people who use tobacco versus those who do not [148]. However, the underlying mechanisms (similar to what could be the case for alcohol) are yet to be understood. While some preclinical studies showed a decrease in the rewarding effects of nicotine as vitamin D signaling increased [25], human studies have not confirmed this [125]. Nonetheless, one preclinical and one clinical study of vitamin D supplementation showed that it could alleviate nicotine withdrawal symptoms, perhaps through its anti-inflammatory effects and/or effects on anxiety [149, 150].

Vitamin D's impact on stimulant use warrants further study. Vitamin D deficiency has been linked to heightened responsiveness to amphetamine and increased amphetamine consumption, and calcitriol administration may reduce consumption [27, 29]. Also, vitamin D may have beneficial effects against methamphetamine-induced neurotoxicity (e.g., serotonin and dopamine depletion) [128, 129]. In clinical settings, no correlation between stimulant use and vitamin D levels has been reported [100];

however, one RCT found vitamin D treatment efficacious for improving psychiatric symptoms in people who use stimulants [130].

Finally, few studies exist investigating cannabis and benzodiazepine use and vitamin D. One preclinical study found that vitamin D-deficient rats showed heightened sensitivity to cannabinoids' acute effects [122]. Clinically, patients receiving OAT who exhibited lower vitamin D levels had more frequent cannabis use [100].

Overall, vitamin D could have potential benefits for a broad range of BAs and SUDs. Despite gaps in knowledge, addressing vitamin D deficiency could be promising as a simple intervention, considering its inexpensive cost, accessibility, and advantageous safety profile [151]. However, it is important to consider the potential risk of vitamin D intoxication and its clinical manifestations, including hypercalcemia. This consideration is particularly important in light of the ongoing uncertainties regarding various doses or durations of exposure examined to date [152]. Also, based on both preclinical and clinical studies, age [25, 101] and sex [25, 27, 87, 89] seem to influence vitamin D's effects, which may also impact interventions.

It is important to note that this review has several limitations. First, there was an unequal distribution of studies, with a significantly greater emphasis on SUDs compared to BAs and ICDs. This imbalance was also evident across different types of research related to each condition, with an overall higher number of clinical studies than preclinical studies. Notably, no RCTs were conducted for any BAs or ICDs, and most clinical studies of SUDs were observational. Additionally, clinical studies exhibited higher quality compared to preclinical studies. These collective observations underscore the limitations in translating the findings into practical implementation.

Second, there was substantial variation in the potential confounding variables considered across studies, often seemingly without due consideration. For example, being female and of specific race/ethnicity, having lower levels of education, and residing in an urban area were linked to lower serum 25(OH)D levels [153, 154]. Additionally, exposure to sunlight, diet and lifestyle considerations, hepatic damage and malabsorption (especially among individuals with alcohol use) [144], employment status, seasonal sampling, appetite alterations with different substances, reduced physical activity [87], and co-occurring depression [155, 156] are all potentially influential factors.

Third, the absence of standardized measures across studies reduces the ability to draw generalized conclusions. For example, varied methodologies encompassing pain threshold evaluations, subjective reporting modalities and self-reported questionnaires, divergent scales quantifying mental well-being, and different techniques for assessing serum vitamin D levels collectively amplify the complexities of synthesizing findings. Moreover, thresholds for defining vitamin D deficiency and sufficiency varied across studies, as did vitamin D intervention forms, dosages, durations, and administration routes. For example, vitamin D supplementation was used as cholecalciferol in one RCT [130], whereas others only noted using vitamin D3 capsules without specifying the active or inactivated vitamin D formula [105-107, 125]. Vitamin D's dosing also widely varied, ranging from 5 µg for two weeks [91] to 50,000 IU for 24 weeks [107], complicating comparisons across studies.

6. Conclusion

Our research suggests that lower serum vitamin D levels are associated with the development and symptom severity of multiple SUDs. This review is the first to explore relationships between vitamin D and a broad spectrum of addiction-related conditions which often share neurobiological and clinical similarities. Most preclinical and clinical studies support the positive role of vitamin D sufficiency in preventing and addressing SUDs. However, the research focus on these conditions has been unevenly distributed. ICDs have not been studied regarding vitamin D, and BAs have been underrepresented in research. Among SUDs, alcohol and opioid use have been more extensively studied, while others, including benzodiazepine, cannabis, and tobacco use, have received less attention.

Future studies are needed on SUDs and especially BAs and ICDs. There is also a need for more studies with higher-quality experimental designs, such as RCTs, as most of the available clinical literature is observational. Additionally, there is an ongoing gap in studies exploring mechanisms underlying vitamin D effects on these conditions. For example, studies using positron emission tomography (PET) with ligands binding to the dopamine receptors could test the capacity of vitamin D to upregulate dopamine receptors or to correct deficits present in some of these conditions, such as low amphetamine-induced dopamine release. Beyond these human laboratory studies, there is a need to identify recommended levels of vitamin D or doses of vitamin D to optimize brain function and to provide the necessary support for developing specific clinical trials involving people with ICDs, BAs, and SUDs.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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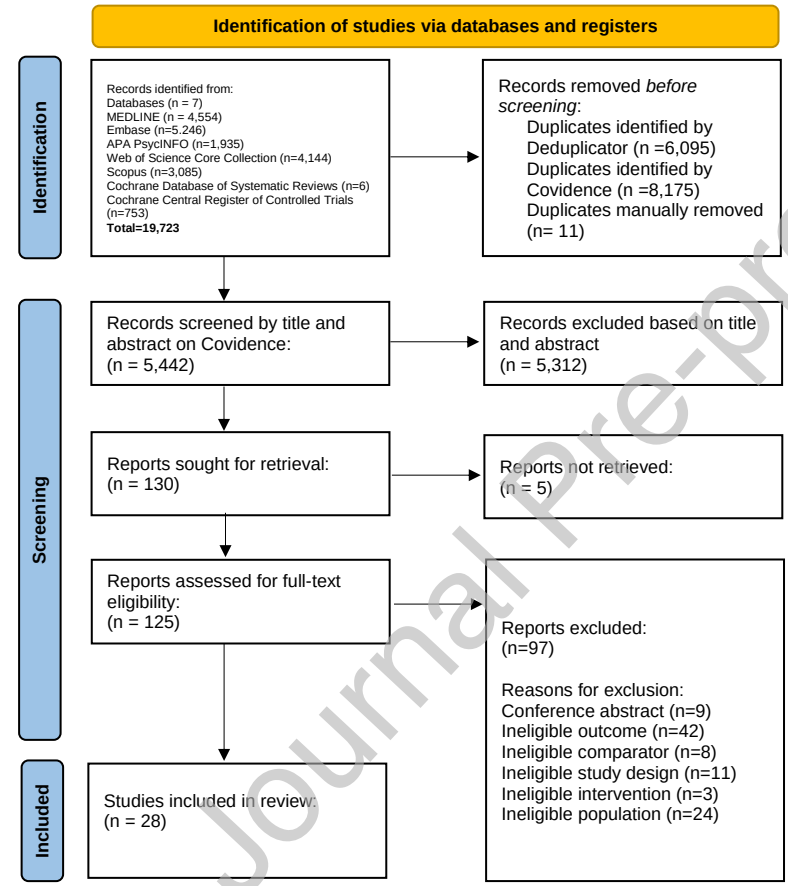

Figure 1. PRISMA diagram of search results

Table 1: Study characteristics included in the scoping review (N=28)

Condition / Substance	Clinical /Preclinical Setting	Author, Year	Country	Study type	Sample characteristics	Type of intervention	Dose, duration, administration route (if applicable)	Adjunctive therapy (Dose, duration, administration route if applicable)	Modality and endpoint	Primary Findings
Gambling Disorder	Preclinical	Peak et al., 2015 [86]	Australia	Preclinical	Sprague-Dawley Rats	Rat Gambling Task	None	None	Behavioral testing	DVD deficiency did not significantly impair decision-making processes in rats. However, subtle alterations in training and performance on the rat gambling task were reported.
Alcohol	Clinical	Neupane et al., 2013 [88]	Norway	Cross-sectional	N = 174, all with AUD	Serum 25(OH)D levels	None	None	Treatment for AUD, socio-demographics, AUD severity, and parameters of alcohol intake	64% of Nepalese patients seeking treatment for AUD had vitamin D deficiency. The degree of deficiency was related to AUD severity. Vitamin D deficiency was less prominent when there was co-occurring depression.
		Lee et al., 2012 [87]	Korea	Cross-sectional	N = 7,010 participants	Vitamin D serum levels measurement	None	None	Sex-specific relationships between vitamin	Sufficiency in Korean men was significantly

									D sufficiency and alcohol consumption	associated with drinking frequency, number of alcoholic drinks consumed, and average daily alcohol intake. No correlation was found in women.
		Wrzosek et al., 2014 [89]	Poland	Case-control	N = 148, all with AUD	Polymorphisms of the vitamin D receptor (VDR) gene using PCR	None	None	Impulsiveness	Genetic variation of the VDR gene is associated with impulsivity in male AUD patients.
		Schuster et al., 2017 [90]	Germany	Cohort	N = 47, all with AUD and undergoing detoxification	Vitamin D serum level measurement	None	None	Psychopathological burden	Low plasma vitamin D concentrations in AUD subjects.
		Schuster et al., 2021 [91]	Germany	RCT	N = 55 all with AUD, 26 (47.2%) of whom received vitamin D	Vitamin D supplement	800 mg + 5 µg vitamin D daily (PO)	Oral calcium carbonate, sodium bicarbonate	Alcohol craving, withdrawal, and relapse risk	Oral calcium administration attenuates withdrawal and reduces craving over a time span of 14 days during inpatient detoxification treatment
Opioids	Preclinical	Bazzani et al., 1983 [108]	Italy	Preclinical	Rats	Vitamin D supplement	Cholecalciferol 1000 IU/Kg/day x 5 days	Morphine (20 mg/Kg)	Pain threshold, morphine analgesic effects, and morphine tolerance	Vitamin D deficiency increased the analgesic effect of morphine and baseline pain threshold. Tolerance to morphine developed faster

										in vitamin-D-deficient rats and these effects were reversed once injected with vitamin D.
		Saeedfar et al., 2023 [109]	Iran	Preclinical	Rats	Vitamin D supplement	Vitamin D in 3 doses (250, 500, and 1000 IU/kg)	Morphine administration	Morphine effects	Vitamin D administration after morphine led to an increase in the place preference index in the acquisition phase.
		Akbari et al., 2023 [110]	Iran	Preclinical	Rats	Vitamin D supplement	Vitamin D in 2 doses (5 and 10 µg/kg))	Morphine administration	the effect of vitamin D on conditioned place preference (CPP) induced by morphine	Administration of a higher concentration of vitamin D (10 µg/kg) prior to morphine conditioning significantly attenuated the expression of morphine-paired context memory. Administration of vitamin D (5 µg/kg) before conditioning did not affect morphine acquisition or expression but facilitated extinction and significantly attenuated morphine reinstatement. Administration of vitamin D after

										the morphine post-conditioning test expedited extinction and significantly attenuated morphine reinstatement.
Opioids	Clinical	Abdolahzade-Arani et al., 2021 [97]	Iran	Cross-sectional	N = 500, all receiving MMT	Vitamin D serum levels measurement	None	MMT	Duration and dosage of MMT, BDI and BAI scores	Non-significant correlation between serum vitamin D levels and MMT dose and duration. Improved BDI and BAI scores with higher vitamin D levels.
		Turner et al., 2008 [98]	USA	Cross-sectional	N = 267, all with chronic pain and admitted to a pain rehabilitation program	Vitamin D serum levels measurement	None	None	Prevalence and effects of vitamin D inadequacy	Significant increase in mean morphine doses and durations in the vitamin-D-inadequate group.
		Bose et al., 2015 [99]	USA	Cross-sectional	N= 185, all with morbid obesity and undergoing bariatric surgery	Vitamin D serum levels measurement	None	None	Time-weighted average of pain scores and total opioid consumption	No significant differences in pain scores and opioid consumption after surgery between groups with vitamin-D-deficient and -sufficient levels.
		Kim et al., 2020 [102]	USA	Cohort	N = 14,356 participants	Vitamin D serum measurement, single level preoperatively	None	None	Opioid use dose and duration and incident opioid use disorder	Vitamin D deficiency was associated with increased number of days of postoperative opioid use and

										higher total opioid dose among opioid-naïve subjects and was associated with incident opioid use disorder within follow-up period.
		Bergman et al., 2015 [101]	Sweden	Cohort	N = 100, all are patients receiving palliative care for cancer	Vitamin D serum measurement	None	None	Changes in opioids dose	Deficient 25(OH)D levels associated with higher opioid use dose.
		Malik et al., 2021 [103]	Israel	Cohort	N = 394, all receiving MMT	Vitamin D serum levels measurement	None	MMT	Outcomes of MMT	Higher vitamin D levels associated with longer cumulative retention in MMT.
		Xia et al., 2022 [104]	China	Cohort	N = 112, all diagnosed with colorectal cancer	Vitamin D serum levels measurement	None	None	Pre- and post-operative pain threshold and opioid consumption	Lower serum vitamin D levels were associated with higher pain sensitivity and lower baseline preoperative pain threshold, higher intraoperative opioid consumption (sufentanil), higher postoperative pain levels, and higher dosage of postoperative patient-controlled fentanyl
		Bemanian	Norway	Cohort	N = 666, all	Vitamin D	None	OAT	Substance use	Lower serum

		et al., 2022 [100]			receiving OAT	serum measurement			severity and OAT	vitamin D concentration at baseline was found for those with more frequent consumption of cannabis. but the time trend was not significant. No significant associations were found for the OAT dose ratio variable.
		Ghaderi et al., 2017 [105]	Iran	RCT	N = 64, all receiving MMT	Vitamin D supplement	50,000 IU vitamin D biweekly for 12 weeks (PO)	MMT	Psychological symptoms	Improved sleep quality and depression.
		Ghaderi et al., 2020 [106]	Iran	RCT	N= 40, all receiving MMT	vitamin D supplement	50,000 IU vitamin D biweekly for 12 weeks (PO)	MMT	Withdrawal symptoms and gene expression	Administration ameliorated IL-1 and PPAR-γ expression but did not impact IL-8 and TNF-α expression and COWS.
		Ghaderi, A et al., 2020 [107]	Iran	RCT	N = 64, all receiving MMT	Vitamin D supplement	50,000 IU vitamin D biweekly for 24 weeks (PO)	MMT (in the form of syrup)	Cognitive functions and mental health parameters	Administration improved BDI, IGT, FAS, LM-Immediate, DGSP-Reverse, and visual working memory, but did not affect BAI, TMT subscales, LM-Delayed and DGSP-Straight.

	Combination of preclinical and clinical	Kemény et al., 2021 [25]	USA	Preclinical, and a clinical cohort	People diagnosed with opioid use disorder and mice	Vitamin D serum levels	None	None	Response to opioids, opioid withdrawal severity, opioid analgesia effects	Preclinically, mice with vitamin D deficiency demonstrated response to morphine at lower doses, had significantly increased basal thermal nociceptive thresholds and greater opioid analgesia effects, mice showed earlier signs of withdrawal manifestation and more significant severity of withdrawal symptoms compared to vitamin D sufficient mice. Clinically, increased prevalence of vitamin D deficiency in patients diagnosed with opioid use disorder and an inverse and dose-dependent association of vitamin D levels with self-reported opioid use.
Cannabis	Preclinical	Burne et al., 2014 [122]	Australia	Preclinical	Rats	Maternal Vitamin D-	None	THC injections	Behavioral effects of THC	DVD-deficient rats showed THC-

						deficient diet				induced enhancement of pre-pulse inhibition. No significant effect on open field activity or DMTS.
Tobacco	Clinical	Bagheri et al., 2022 [125]	Iran	RCT	N = 60, all with tobacco misuse	Vitamin D supplement	50,000 IU biweekly for 2 weeks (PO)	None	Nicotine misuse	No significant effect of vitamin D administration on nicotine misuse.
Stimulants	Preclinical	Kesby et al., 2009 [27]	Australia	Preclinical	Rats	Vitamin D-deficient diet for 6 weeks	None	None	locomotor responses to different doses of amphetamine	In females only, DVD-deficient adult rats displayed an enhanced sensitivity to amphetamine-induced locomotion, an increased dopamine transporter density in the caudate/putamen and increased affinity in the nucleus accumbens.
		Cass et al., 2006 [128]	USA	Preclinical	Rats	calcitriol diet	(1μg/kg) x1 day for 8 days	methamphetamine (5 mg/kg, s.c.)	methamphetamine-induced reductions in striatal and nucleus accumbens levels of DA and 5-HT.	Significant reduction of methamphetamine-induced dopamine release in rats treated with both methamphetamine and calcitriol, compared to methamphetamine only. No

										reduction in hyperthermia.
		Cass et al., 2023 [129]	USA	Preclinical	Rats	Vitamin D (calcitriol s.c.)	calcitriol 0.3, 1.0, and 3.0 µg/kg/day.	methamphetamine (5 mg/kg, s.c.)	level of striatal serotonin (5-HT) release and content following treatment with neurotoxic doses of methamphetamine and calcitriol	Calcitriol demonstrated protective effects against methamphetamine-induced reductions in striatal serotonin levels. Vitamin D supplementation at doses of 1.0 and 3.0 µg/kg/day increased basal extracellular levels of the primary 5-HT metabolite, 5-hydroxyindole acetic acid, and mitigated reductions in 5-HT overflow induced by methamphetamine treatment.
	Clinical	Lubis et al., 2019 [130]	Pakistan	RCT	N = 50, all with ATS use		1000 IU vitamin D daily for 42 days (PO)	None	BPRS score	Higher BPRS scores in the intervention group.
	Preclinical	Trinko et al., 2016 [29]	USA	Preclinical	Rats	Vitamin D supplement	calcitriol, 10 µg/kg	acute single administration of amphetamine (2.5 mg/kg, intraperitoneal)	Drug seeking behavior and tonic and phasic dopamine release	Vitamin-D-deficient vs. vitamin-D-sufficient diets were linked to more amphetamine-seeking behaviors. Acute calcitriol administration

										reduced amphetamine consumption and enhanced neurochemical and behavioral responses to acute amphetamine administration.

AD, alcohol dependent; ATS, Amphetamine-Type Stimulants; AUDs, Alcohol Use Disorders; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BPRS, Brief Psychiatric Rating Scale; COWS, Clinical Opiate Withdrawal Scale; CP, chronic pain; D3, Vitamin D; DGSP Reverse, Digit Span Reverse; DGSP-Straight, Digit Span Straight; DMTS, Delayed Matching to Sample task; DRD2-GDNF, Dopamine receptor D2-Glial cell line-derived neurotrophic factor; DVD; developmental vitamin D; 25(OH)D, 25-Hydroxyvitamin D; FAS, Frontal Assessment Battery; GDNF, Glial cell line-derived neurotrophic factor; IGT, Iowa Gambling Task; IL-1, Interleukin-1; IL-8, Interleukin-8; LM-Delayed, Logical Memory-Delayed; LM-Immediate, Logical Memory-Immediate; MMT, methadone maintenance treatment; OAT, opioid agonist therapy; ODP, opioid-dependent patients; PCR, Polymerase Chain Reaction; PO, oral; PPAR-γ, Peroxisome proliferator-activated receptor gamma; RCT, Randomized-Controlled Trial; THC, Tetrahydrocannabinol; TMT, Trail Making Test; TNF-α, Tumor necrosis factor-alpha; UV, ultraviolet radiation; VDR, vitamin D receptor.