Journal of Psychiatric Research 129 (2020) 250–256

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

# Effect of adjunctive single dose parenteral Vitamin D supplementation in major depressive disorder with concurrent vitamin D deficiency: A double-blind randomized placebo-controlled trial

Favaz Vellekkatt [a], Vikas Menon [a,*], Medha Rajappa [b], Jayaprakash Sahoo [c]

[a] Department of Psychiatry, Jawaharlal Institute of Post Graduate Medical Education and Research (JIPMER), Puducherry, 605006, India
[b] Department of Biochemistry, Jawaharlal Institute of Post Graduate Medical Education and Research (JIPMER), Puducherry, 605006, India
[c] Department of Endocrinology, Jawaharlal Institute of Post Graduate Medical Education and Research (JIPMER), Puducherry, 605006, India

ARTICLE INFO

*Keywords:*
Adjunctive treatment
Quality of life
Neuroinflammation
Major depression
Vitamin D
Randomized controlled trial

ABSTRACT

Adjunctive vitamin D replacement is a theoretically promising strategy to improve outcomes in major depression. Our objective was to assess the efficacy of a single parenteral dose of vitamin D supplementation at baseline as an adjunct to treatment as usual on change in depression symptom ratings (primary outcome), quality of life and clinical severity of illness (secondary outcomes) at the end of 12 weeks when compared to treatment as usual in patients with major depression and concurrent Vitamin D deficiency. Eligible participants were randomized to receive either treatment as usual (TAU; n = 23) or TAU plus single parenteral dose of 3,00,000 IU of vitamin D (n = 23) at baseline. Rater-blinded assessments of depression (primary outcome), quality of life (QoL) and clinical severity of illness were obtained at baseline, and end of follow-up (12 weeks). Intent-to-treat analyses were performed on the entire randomized sample. The intervention significantly improved depression symptom ratings, quality of life and clinical severity of illness at the end of the treatment phase. These findings indicate that a single parenteral dose (3,00,000 IU) of adjunctive vitamin D replacement at baseline is an effective and well tolerated intervention in major depressive disorder with concurrent Vitamin D deficiency. Additionally, it points to a possible role for vitamin D in the pathophysiology of depression and supports personalized approaches for treatment of major depressive disorder.

## 1. Introduction

The treatment of major depressive disorder (MDD) continues to pose an enormous challenge to clinicians. According to data from the Sequenced Treatment Algorithm to relieve Depression (STAR*D) trial, only 37% of patients with major depression remit with the first anti-depressant trial with increasing treatment resistance noted for subsequent anti-depressant trials (Rush et al., 2006). This means that nearly two-thirds of patients with MDD do not have a satisfactory response to anti-depressants. The impact of partial or non-response in MDD include biological, humanistic and economic consequences such as increased risk of structural brain changes, neuroprogression, relapse, poor quality of life, work absenteeism and productivity losses to the tune of over 50 billion dollars annually (Israel, 2010; Lorenzetti et al., 2009; Mauskopf et al., 2009; Moylan et al., 2013; Zajecka et al., 2013). This indicates the importance of "early optimized treatment" in depression.

One such strategy that has been receiving increasing clinical and research attention, of late, is supplementing vitamin D in the acute phases of depression. Biologically, vitamin D deficiency may predispose to depression through its effects on neuronal calcium homeostasis, immune system signalling as well as gene and protein expressions (Berridge, 2017; White, 2012). These processes augment inflammatory responses that may have "depressogenic" effects (Felger, 2018; Mangin et al., 2014). Juxtaposing these findings together with the known anti-inflammatory properties of vitamin D (Hashemi et al., 2018; Liu et al., 2018), a strong case can be made for vitamin D as a potential adjunctive therapy for MDD.

Existing studies, thus far, show conflicting evidence for the therapeutic efficacy of supplemental vitamin D on depressive symptoms (Bertone-Johnson et al., 2012; Dean et al., 2011; Jorde et al., 2008). Lessons from a failed trial on patients with non-remitted MDD support designing trials that evaluate vitamin D as an adjunct to standard

* Corresponding author.
*E-mail addresses:* favazvkptaj@gmail.com (F. Vellekkatt), drvmenon@gmail.com (V. Menon), linkmedha@gmail.com (M. Rajappa), jppgi@yahoo.com (J. Sahoo).

https://doi.org/10.1016/j.jpsychires.2020.07.037
Received 29 January 2020; Received in revised form 19 July 2020; Accepted 25 July 2020
Available online 4 August 2020

treatment in MDD as this may pre-empt issues of confounding with high rates of co-morbidity and multiple medications (Aucoin et al., 2018). Clinical heterogeneity among subjects with respect to vitamin D status or depression could also impact findings (Menon et al., 2020; Spedding, 2014).

The present study is designed to add to the ongoing discussion in this area with two key methodological additions informed by evidence; firstly, we study only subjects clinically diagnosed with major depression and concurrent vitamin D deficiency (Menon et al., 2020) and secondly, we attempt to minimize possible issues with compliance by using single dose parenteral vitamin D supplementation (300,000 IU) (Mozaffari-Khosravi et al., 2013; Zanetidou et al., 2011).

We aimed to assess the efficacy of a single parenteral dose (300,000 IU) vitamin D supplementation (intervention) at baseline as an adjunct to treatment as usual on change in depression symptom ratings (primary outcome), quality of life and clinical severity of illness (secondary outcomes) at the end of 12 weeks when compared to treatment as usual in depressed patients with concurrent Vitamin D deficiency.

## 2. Material and methods

### 2.1. Setting, design and participant selection

This was a double-blind randomized parallel arm placebo-controlled trial carried out in collaboration between the departments of Psychiatry, Biochemistry and Endocrinology at Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India. JIPMER is a centrally funded university hospital in South India providing highly subsidized medical care to service users.

The department of Psychiatry at the institute is a typical general hospital psychiatry unit and offers both outpatient and inpatient services. All patients attending the walk-in clinic are evaluated in two sequential steps; initially they are screened by a senior resident (qualified psychiatrist equivalent to registrar) for psychiatric morbidity and immediate management is offered to those who need it. Subsequently, they are evaluated in detail by a post graduate trainee on appointment basis, after which the case is discussed with the consultant psychiatrist to formulate the case from a diagnostic and management standpoint.

Between October 2017 to April 2019, we assessed all consecutive subjects aged between 18 and 65 years who were diagnosed with major depressive disorder using DSM-5 criteria (American Psychiatric Association, 2013) for their eligibility to be included into the study. In all of them, the diagnosis was additionally confirmed using M.I.N.I (Mini international neuropsychiatric interview)-Plus 6.0 (Sheehan et al., 1998). For inclusion into the study, patients should have had assay positive vitamin D deficiency (defined as Serum 25-hydroxyvitamin D $< 20$ ng/mL) (Rosen et al., 2012), should not have been exposed to anti-depressants in the last 6 weeks and had to provide written informed consent. We excluded pregnant or lactating mothers, people with known cardiovascular, renal and hepatic diseases or those on vitamin D or other nutritional supplements in the last 3 months. Patients with clinical manifestations of vitamin D deficiency were also excluded due to ethical reasons.

Ethical clearance was obtained from the Institute Human Ethics Committee (IEC). Trial registration was done with the Clinical Trial Registry of India (CTRI) [CTRI/2017/09/009824].

### 2.2. Assessments

Following strict aseptic precautions, 3 ml venous sample was drawn for assessing 25-hydroxyvitamin D status from all subjects with major depression prior to initiating any treatment. Subsequently, they were rated at baseline on the following outcome measures by a blinded rater:

1. Hamilton Depression rating scale-17 (HDRS-17) (Hamilton, 1960) (primary outcome) – This is a clinician administered questionnaire widely used to rate the clinical severity of depression, as well as a guide to evaluate recovery. Each of the 17 items on the questionnaire is scored either on a 3-point or 5-point Likert type scale. A score of 0–7 is considered to be within normal range (or clinical remission) while the following severity ranges have been posited: mild depression (8–16); moderate depression (17–23); and severe depression ($\geq$24).
2. Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (QLES) (Endicott et al., 1993) (secondary outcome) - This 16-item self-report measure is designed to assess the degree of satisfaction or enjoyment experienced by the respondent in the past week. [19] The total score for the first 14 items is calculated and expressed as a percentage of the maximum score of 70. The last two items are standalone items and are not included in the overall scoring. The scale has robust psychometric properties (Cronbach's alpha 0.9 and test-retest reliability of 0.86) and has previously been used to assess the quality of life impairment in depressed subjects (Endicott et al., 1993; Rapaport et al., 2005).
3. Clinical Global Impression (CGI) severity of illness (CGI-S) (Guy, 1976) (secondary outcome) - It is a 3-item observer-rated scale which measures the severity of illness, global improvement or change, and therapeutic response. It asks the clinician to rate the patient relative to past experience with other patients with the same diagnosis.

Subsequent to the above assessments, patients were initiated on antidepressants and other elements of standard care (including psychotherapy) as appropriate by an independent physician not involved in other aspects of the study.

The blood samples were assessed by chemiluminescence using Beckman Coulter DXI Chemiluminescent Assay System, which uses a closed kit. Assays were done in duplicate to increase reliability and validity of measurement. All individuals with normal vitamin D levels were excluded from further aspects of the trial (Serum 25-hydroxyvitamin D $\geq$ 20 ng/ml) (Rosen et al., 2012). They continued to receive routine care as appropriate from the mood disorder follow-up clinic.

Included study participants (those with depression and vitamin D deficiency) were randomized into intervention or control groups using a computer-generated random number sequence. A stratified permuted block design was used to ensure balanced allocation of inpatients and outpatients between groups; this was because we believed that inpatient versus outpatient status could influence prognosis. The block size was uniformly set at four. Allocation concealment was effected using sequentially numbered opaque sealed envelopes that were maintained by an investigator who was not involved in any other aspect of the study.

Next, the intervention group received 300,000 I.U. of cholecalciferol (Arachitol) injection (intervention) while the control group received 1 ml normal saline injection (placebo), both given intramuscularly in the gluteal region. Following this, all participants were advised to come regularly to the mood disorder follow-up clinic to collect their drug refills once in three weeks which is part of standard care. During their outpatient visits, patients were enquired about adverse effects due to the intervention and given instructions to maintain regular follow-up. For those who did not present themselves physically for follow-up despite these instructions, two telephonic reminders were given three days apart. No further reminders were sent to those who did not respond.

At 12 weeks ($\pm$1 week), rater-blinded assessments were re-obtained for primary and secondary outcome measures. For those who did not follow-up physically, telephonic assessments using mobile phone-based voice calls were used to obtain outcome measures data. Additionally, adherence to anti-depressant medications were assessed at follow-up using the four-item Morisky Green Levine Medication Adherence Scale (MGLS) (Morisky et al., 1986). The scale scores range from 0 to 4 with each item eliciting a yes/no response. High, medium and low adherence has been defined as 0, 1–2 and 3–4 respectively.

At the end of the study (12 weeks), change in outcome parameters was computed and compared between groups. For in-patients, the same

procedure and periodicity were followed for data collection until discharge, after which they were followed up as outpatients till the end of 12 weeks. Following the completion of study period, vitamin D injections were provided to control group participants as part of post-trial responsibilities of the investigator.

### 2.3. Sample size calculation

Using a power of 90% and precision level of 5%, a sample size of 19 was required in each group to detect an expected mean difference of 7.2 (Standard Deviation (SD)1 = 3.8 and SD2 = 8.7) between the two groups on primary outcome measure (HDRS-17) based on previous studies (Mozaffari-Khosravi et al., 2013), using open source OpenEpi software version 3.01. To account for lost to follow-up, 23 subjects (all with assay positive vitamin D deficiency) were recruited in each group (total n = 46).

### 2.4. Statistical analysis

Mean with standard deviation or median with interquartile range was used to express continuous variables depending on normality of data, assessed by the Shapiro-Wilk test. Categorical variables were depicted using frequencies and percentages. Comparison of continuous and categorical variables at baseline between groups was done using independent samples *t*-test/Mann-Whitney *U* test and chi-square test respectively. Adherence scores were dichotomized as low or high (including medium and high). Bivariate correlation (pearson r or spearman rho, based on distribution of data) was used to assess correlation between baseline vitamin D status and clinical severity of depression.

Primary analysis examined the Intention-to-treat (ITT) sample, defined as every subject initially randomized irrespective of protocol deviations or attrition. Two sensitivity analyses were planned a priori; first, examining the completer samples and second, excluding telephonic follow-ups. Missing values for dropouts were imputed using the last observation carried forward method (LOCF).

Change scores for outcome measures were computed by deducting the 12-week score from the baseline score. Analysis of covariance (ANCOVA) of these change scores was performed to identify the effect of group assignment on outcomes, while simultaneously controlling for the effect of baseline scores.

## 3. Results

### 3.1. Sample description (Table 1)

Age of the sample (n = 46) ranged from 18 to 63 years. The mean age (standard deviation) was 35.9 (±11.6) years. The sample predominantly comprised of subjects aged less than 40 years (n = 29, 63.0%). Table 1 depicts the demographic and clinical description of the sample. No differences were noted between the intervention and control groups, at baseline, on either the socio-demographic, clinical or outcome parameters (data available from authors on request). Nine participants had medical co-morbidities such as anaemia (n = 3), hypothyroidism (n = 2), osteoarthritis (n = 1), optic atrophy (n = 1), poliomyelitis (n = 1) and post-cerebrovascular accident (n = 1). Alcohol use disorder and nicotine use disorder were seen in three and two participants respectively.

### 3.2. Sample disposition (Fig. 1)

The flow of patients throughout the study period is shown in Fig. 1. A total of 86 patients with major depression had to be screened in order to get 46 eligible and consenting participants. At the end of the study (12 weeks), 4 participants had dropped out; 1 and 3 from the intervention and control groups, respectively. The proportion of patients who dropped out were comparable between groups ($\chi 2 = 0.13$, p = 0.72). At follow-up, no between-group differences were noted in adherence to oral anti-depressants ($\chi 2 = 0.11$, p = 0.75).

There were no significant baseline differences between completer and lost to follow-up groups on demographic, clinical or outcome parameters (data available from authors on request). Physical follow-up data were available for 32 out of 42 study completers while

**Table 1**
Demographic and clinical description of the sample.

| Variable | | Cases (n = 23) | Controls (n = 23) |
|---|---|---|---|
| Age (years)* | | 36.2 (12.3) | 35.8 (11.2) |
| Gender | Male | 6 (26.1%) | 9 (39.1%) |
| Education$^{+}$ | | 8 (6–13) | 9 (7–12) |
| Occupation | Employed | 7 (30.4%) | 8 (34.8%) |
| Marital status | Married | 19 (82.6%) | 16 (69.6%) |
| Socio-economic status | | | |
| Low | | 13 (56.5%) | 15 (65.2%) |
| Domicile | Rural | 18 (78.3%) | 14 (60.9%) |
| Medical co-morbidity | | 3 (13.0%) | 6 (26.1%) |
| Substance dependence | | 1 (4.3%) | 4 (17.4%) |
| Diagnosis | | | |
| Severe Depression | | 8 (34.8%) | 6 (26.1%) |
| Recurrent Depression | Yes | 3 (13.0%) | 7 (30.4%) |
| Inpatient | Yes | 4 (17.4%) | 4 (17.4%) |
| Lifetime h/o Suicide attempt | | | |
| | | 5 (21.7%) | 4 (17.4%) |
| Body mass index | | 21.9 (4.2) | 23.8 (5.6) |
| Time spent outdoors$^{+}$ (min/week) | | | |
| | | 30.0 (22.5–63.7) | 37.5 (25.0–43.7) |
| Adherence | Low | 4 (18.2%) | 3 (15.0%) |
| Antidepressant | | | |
| Fluoxetine | | 22 (95.7%) | 19 (82.6%) |
| Amitryptiline | | 1 (4.3%) | 0 (0.0%) |
| Escitalopram | | 0 (0.0%) | 3 (13.0%) |
| Mirtazepine | | 0 (0.0%) | 1 (4.3%) |

Values expressed as *mean (standard deviation), $^{+}$median (interquartile range) or frequency (%).

**Table 2**
Depression scores across the study in intervention versus control groups.

| Depression scores | Intervention | Control | t or U, df, P-value |
|---|---|---|---|
| Baseline | 19.4 (±4.0) | 17.44 (±3.1) | −1.92, 44, 0.061 |
| Three months | 3.0 (2.0–4.0) | 5.0 (3.2–8.0) | 89.00, 40, 0.001* |

Values for intervention and control groups are mean (standard deviation) or median (interquartile range); Comparisons done using independent student *t*-test or Mann-Whitney *U* test; *significant at p < 0.05.

**Table 3**
Quality of life scores across the study in intervention versus control groups.

| Quality of life scores | Intervention | Control | t, df, P-value |
|---|---|---|---|
| Baseline | 27.6 (±5.7) | 30.6 (±6.0) | 1.71, 44, 0.095 |
| Three months | 50.9 (±7.1) | 42.1 (±6.1) | −4.48, 40, <0.001* |

Values for intervention and control groups are mean (standard deviation); Comparisons done using independent student *t*-test; *significant at p < 0.05.

**Table 4**
Clinical severity of illness scores across the study in intervention versus control groups.

| Clinical severity of illness scores | Intervention | Control | t or U, df, P-value |
|---|---|---|---|
| Baseline | 5.4 (±0.9) | 5.1 (±0.7) | 1.71, 44, 0.095 |
| Three months | 1.0 (1.0–2.0) | 3.0 (2.0–4.0) | 90.50, 40, <0.001* |

Values for intervention and control groups are mean (standard deviation) or median (interquartile range); Comparisons done using independent student *t*-test or Mann-Whitney *U* test; *significant at p < 0.05.

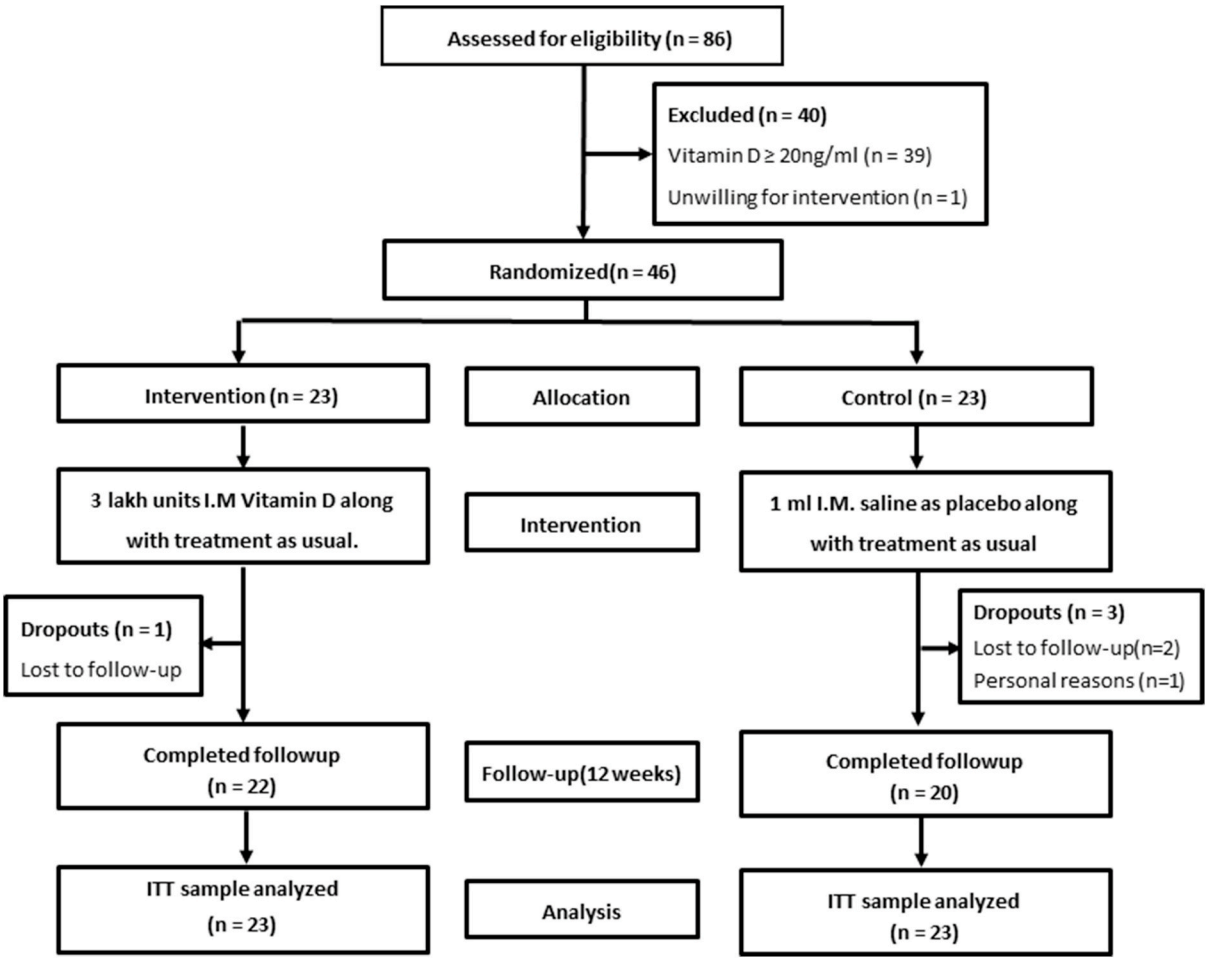


**Fig. 1.** Consolidated Standards of Reporting Trials (CONSORT) flow diagram for the trial.

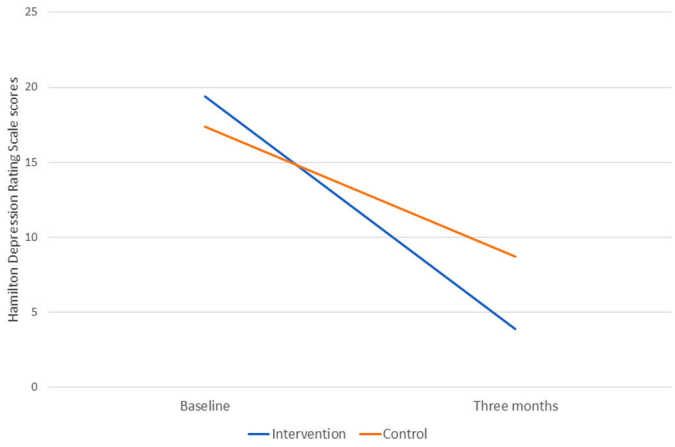


**Fig. 2.** Depression symptom ratings across the study in the intervention and control groups.

telephonic follow-up data were available for the remaining 10. No major adverse effects were reported by any of the participants.

### 3.3. Correlation between vitamin D status and depression at baseline

Serum 25-hydroxyvitamin D levels, at baseline, did not significantly correlate with baseline depression ratings, both among the total screened sample (n = 85, Pearson r = −0.06, p = 0.59) as well as included trial participants (n = 46, Spearman's rho = 0.26, p = 0.076).

### 3.4. Primary outcome: depression (Table 2, Fig. 2)

The intervention was associated with significant improvement in depression scores at the end of 12 weeks in the ITT (F = 11.55, df = 1,44, p = 0.001, partial eta square = 0.21) as well as the completer analysis (F = 12.93, df = 1,40, p = 0.001, partial eta square = 0.25). This finding showed that the adjunctive vitamin D intervention was effective in improving depression symptom ratings among the cases. The results continued to remain significant in the sensitivity analysis excluding telephonic follow-ups (F = 7.01, df = 1,30, p = 0.01, partial eta square = 0.12).

### 3.5. Secondary outcome: quality of life (Table 3)

The intervention was associated with significant improvement in quality of life scores at the end of 12 weeks in both the ITT (F = 28.06, df = 1,44, p < 0.001, partial eta square = 0.39) and completer analysis (F = 34.35, df = 1,40, p < 0.001, partial eta square = 0.47). This finding showed that the adjunctive vitamin D intervention was effective in improving the quality of life among the cases. The findings continued to remain significant in the sensitivity analysis excluding telephonic follow-ups (F = 27.24, df = 1,30, p < 0.001, partial eta square = 0.48).

### 3.6. Secondary outcome: clinical severity of illness (Table 4)

The intervention was associated with significant improvement in

clinical severity of illness (depression) at the end of 12 weeks in both the ITT ($F = 14.41$, $df = 1,44$, $p < 0.001$, partial eta square $= 0.25$) and completer analysis ($F = 14.97$, $df = 1,40$, $p < 0.001$, partial eta square $= 0.28$). This finding showed that the adjunctive vitamin D intervention was effective in improving the clinical severity of illness among cases. The findings continued to remain significant in the sensitivity analysis excluding telephonic follow-ups ($F = 34.02$, $df = 1,30$, $p < 0.001$, partial eta square $= 0.54$).

## 4. Discussion

### 4.1. Summary of findings

A single parenteral dose of 300,000 IU of vitamin D supplementation was effective in improving depression symptom ratings at the end of 12 weeks among subjects with major depression and concurrent vitamin D deficiency. Further, the intervention also significantly improved quality of life and clinical severity of illness ratings.

### 4.2. Interpretation of findings

Previous studies (Jorde et al., 2008; Kjærgaard et al., 2012; Yalamanchili and Gallagher, 2012), all of them examining the effects of oral vitamin D supplementation on depressive symptoms, have shown conflicting results. These differences could be attributed to variations in study design, sample characteristics (clinical vs. non-clinical depression), vitamin D status (normal vs. deficient vs. insufficient), study setting (hospital vs. community based), age group studied, dose, duration and frequency of vitamin D supplementation as well as outcome measures used.

Interestingly, four randomized controlled trials (RCT) (Khoraminya et al., 2013; Mozaffari-Khosravi et al., 2013; Sepehrmanesh et al., 2016; Wang et al., 2016), that examined the effects of supplemental vitamin D in clinical depression, showed clinical benefits ranging from a low to moderate effect size while two RCT's (Choukri et al., 2018; Jorde and Kubiak, 2018), which studied non-clinical subjects, were negative.

The one prior study, which also examined effect of parenteral supplementation of vitamin D in clinical depression, noted positive results (Mozaffari-Khosravi et al., 2013). However, in this study, subjects were not concurrently given anti-depressants. In fact, those who had to be initiated on anti-depressants after entering the study were excluded from final analysis. Therefore, it is possible that many participants might had milder varieties of depression, or, at the very least, may have been clinically heterogenous with respect to severity of depression, unlike our sample. The present study builds on these results by demonstrating a clinical benefit of parenteral vitamin D over and above standard anti-depressant therapy, which is a finding of clinical relevance.

Our findings, when combined with the results of three meta-analyses (Gowda et al., 2015; Spedding, 2014; Vellekkatt and Menon, 2019) on effect of vitamin D supplementation in depression, indicate that vitamin D supplementation in depression may be most effective in clinically depressed subjects with co-morbid vitamin D deficiency. In other words, just as inflammation and anti-inflammatory agents may not be relevant for all cases of depression (Amodeo et al., 2017; Berk et al., 2013; Krishnadas and Cavanagh, 2012), there appears to be a sub-group of depressed patients in whom vitamin D supplementation may be more effective. This presents significant opportunities for researchers.

Another pertinent issue is that of compliance with oral vitamin D supplementation regimens which may warrant daily or weekly dosing. Sub-optimal adherence to psychiatric and medical treatments is substantial in major depression (DiMatteo et al., 2000; Martin-Vazquez, 2016). Some of the previous vitamin D trials in depression with negative results have shown inadequate rise or fall in vitamin D levels post-intervention, partly attributed to poor adherence (Spedding, 2014). This issue can be mitigated, to an extent, with single dose parenteral supplementation regimens.

No correlation was observed between baseline vitamin D levels and clinical depression ratings. In this regard, findings from literature mostly support an inverse correlation between vitamin D concentration and depression (Anglin et al., 2013); however, negative studies (Chan et al., 2011; Pan et al., 2009) also exist. Small sample size and preponderance of younger patients (in whom, the relationship is weaker [Parker et al., 2017]) in our sample may be potential reasons for this unexpected finding. In addition, this was not a population-based study and prior hospital-based studies have shown conflicting results in this regard (Schneider et al., 2000). Nevertheless, given that the two available negative studies were also from similar monsoon-influenced tropical regions, the role of geographical factors in moderating the association between vitamin D and depression must be considered.

Not many prior studies have assessed quality of life as an outcome variable while studying the effect of adjunctive vitamin D supplementation in major depression. More than a decade ago, a review suggested that treatment of deficient vitamin D levels in persons with depression could potentially improve health outcomes and quality of life (Penckofer et al., 2010). More recent reviews have reported a lack of benefits for vitamin D supplementation on quality of life; however, in clinical populations, they do appear to have some benefits (Hoffmann et al., 2015). These observations tally with the beneficial effects of supplemental vitamin D on quality of life in major depression found in the present study. More studies are needed to assess the effect of vitamin D on quality of life in major depression and whether these effects are age and gender-specific.

### 4.3. Limitations and strengths of the study

First, this was a single centre trial carried out at a tertiary care centre and the results may not necessarily generalize to other settings. Second, we have not assessed post-trial vitamin D status of the participants and are, therefore, unable to comment on the association between change in vitamin D status and clinical improvement noted. This may have given a more complete picture about the role of intervention in clinical improvement and must be addressed by future investigators. In this regard, investigators may also consider assessment of serum calcium and phosphorus levels; this would be useful in understanding whether the effects of vitamin D on the brain are independent of the homeostatic pathways that regulate serum calcium and phosphorus. Third, the durability of the observed therapeutic benefits is unanswered as the trial was for a relatively short duration. Fourth, the primary outcome measure (HDRS-17) used in the study has many items that refer to somatic symptoms. It is probable that these symptoms may have preferentially responded to the vitamin D supplementation and this may have contributed to the observed improvement. Future research must assess improvements in other symptom dimensions of depression, such as cognition, as this will give a better understanding of the mechanistic pathways that underlie the observed therapeutic benefits of adjunctive vitamin D in major depression.

Study strengths include design, stratification for locus of treatment in depression and a priori power calculation. We studied only patients with concurrent major depression and vitamin D deficiency; an approach suggested previously (Menon et al., 2020). The intervention was a one-time parenteral injection given under supervision thus eliminating issues with adherence. Adherence to oral antidepressants was assessed using a standardized scale and were comparable between groups. Further, a placebo response is ruled out because the control group received an identical placebo injection.

### 4.4. Study implications and conclusion

Drawing upon our findings, we offer a few recommendations for future vitamin D supplementation trials in major depression. Investigators must attempt to enrich their sample with clinically depressed subjects who also have laboratory proven vitamin D deficiency. A single

parenteral dose of 300,000 IU of vitamin D may be considered to minimize issues with compliance. Given the anti-inflammatory properties of vitamin D (Liu et al., 2018), researchers must make efforts to concurrently study inflammatory markers in order to uncover potential mediators of the observed benefits in depression. Finally, given the neuroprogression associated with residual depressive symptoms (Moylan et al., 2013), there may be scientific merit in considering adjunctive vitamin D supplementation as a therapeutic step-up strategy in patients with first episode depression and co-morbid vitamin D deficiency.

To conclude, a single parenteral dose of 300,000 IU of vitamin D is an effective adjunct in the treatment of major depression and improves depression symptom ratings as well as quality of life in the short term. Hence, this may be a viable step-up strategy to enhance treatment gains in major depression with concurrent vitamin D deficiency. These encouraging preliminary findings warrant replication across settings and longer periods of follow-up as well as identification of patient subgroups most likely to benefit from these approaches.

## Registration number for clinical trials

The clinical trial protocol was registered with the Clinical Trials Registry of India (CTRI) with registration no CTRI/2017/09/009824.

## Author statement

**Favaz Vellekkatt:** Conceptualization, Data curation, Writing - original draft, literature review, data collection, writing first draft. **Vikas Menon:** Conceptualization, Data curation, Formal analysis, Writing - original draft, Co-conceptualization, literature review, data analysis and revision of draft. **Medha Rajappa:** Conceptualization, Data curation, Writing - original draft, Writing - review & editing, Co-conceptualization, data collection and review of manuscript draft. **Jayaprakash Sahoo:** Conceptualization, Data curation, Writing - original draft, Writing - review & editing, Co-conceptualization, data collection and review of manuscript draft. All authors read and approved the final version of the manuscript.

## Declaration of competing interest

The authors declare no conflicts of interest relevant to the contents of the manuscript.

## Acknowlegements

This work was supported by a grant from the Jawaharlal Institute of Post Graduate Medical Education and Research (JIPMER) intramural research fund (Sanction No: JIPMER/01/135/2017/00661).

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2020.07.037.

## References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th Revised edition. American Psychiatric Association Publishing, Washington, D.C.

Amodeo, G., Trusso, M.A., Fagiolini, A., 2017. Depression and inflammation: disentangling a clear yet complex and multifaceted link. Neuropsychiatry 7, 448–457. https://doi.org/10.4172/Neuropsychiatry.1000236.

Anglin, R.E.S., Samaan, Z., Walter, S.D., McDonald, S.D., 2013. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. Br. J. Psychiatry 202, 100–107. https://doi.org/10.1192/bjp.bp.111.106666.

Aucoin, M., Cooley, K., Anand, L., Furtado, M., Canzonieri, A., Fine, A., Fotinos, K., Chandrasena, R., Klassen, L.J., Epstein, I., Wood, W., Katzman, M.A., 2018. Adjunctive Vitamin D in the treatment of non-remitted depression: lessons from a failed clinical trial. Compl. Ther. Med. 36, 38–45. https://doi.org/10.1016/j.ctim.2017.09.011.

Berk, M., Williams, L.J., Jacka, F.N., O'Neil, A., Pasco, J.A., Moylan, S., Allen, N.B., Stuart, A.L., Hayley, A.C., Byrne, M.L., Maes, M., 2013. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med. 11, 200. https://doi.org/10.1186/1741-7015-11-200.

Berridge, M.J., 2017. Vitamin D and depression: cellular and regulatory mechanisms. Pharmacol. Rev. 69, 80–92. https://doi.org/10.1124/pr.116.013227.

Bertone-Johnson, E.R., Powers, S.I., Spangler, L., Larson, J., Michael, Y.L., Millen, A.E., Bueche, M.N., Salmoirago-Blotcher, E., Wassertheil-Smoller, S., Brunner, R.L., Ockene, I., Ockene, J.K., Liu, S., Manson, J.E., 2012. Vitamin D supplementation and depression in the women's health initiative calcium and vitamin D trial. Am. J. Epidemiol. 176, 1–13. https://doi.org/10.1093/aje/kwr482.

Chan, R., Chan, D., Woo, J., Ohlsson, C., Mellström, D., Kwok, T., Leung, P., 2011. Association between serum 25-hydroxyvitamin D and psychological health in older Chinese men in a cohort study. J. Affect. Disord. 130, 251–259. https://doi.org/10.1016/j.jad.2010.10.029.

Choukri, M.A., Conner, T.S., Haszard, J.J., Harper, M.J., Houghton, L.A., 2018. Effect of vitamin D supplementation on depressive symptoms and psychological wellbeing in healthy adult women: a double-blind randomised controlled clinical trial. J. Nutr. Sci. 7, e23. https://doi.org/10.1017/jns.2018.14.

Dean, A.J., Bellgrove, M.A., Hall, T., Phan, W.M.J., Eyles, D.W., Kvaskoff, D., McGrath, J. J., 2011. Effects of vitamin D supplementation on cognitive and emotional functioning in young adults – a randomised controlled trial. PloS One 6, e25966. https://doi.org/10.1371/journal.pone.0025966.

DiMatteo, M.R., Lepper, H.S., Croghan, T.W., 2000. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient Adherence. Arch. Intern. Med. 160, 2101–2107. https://doi.org/10.1001/archinte.160.14.2101.

Endicott, J., Nee, J., Harrison, W., Blumenthal, R., 1993. Quality of life enjoyment and satisfaction questionnaire: a new measure. Psychopharmacol. Bull. 29, 321–326.

Felger, J.C., 2018. In: Macaluso, M., Preskorn, S.H. (Eds.), Role of Inflammation in Depression and Treatment Implications, Antidepressants. Springer International Publishing, Cham, pp. 255–286. https://doi.org/10.1007/164_2018_166.

Gowda, U., Mutowo, M.P., Smith, B.J., Wluka, A.E., Renzaho, A.M.N., 2015. Vitamin D supplementation to reduce depression in adults: meta-analysis of randomized controlled trials. Nutrition 31, 421–429. https://doi.org/10.1016/j.nut.2014.06.017.

Guy, W., 1976. ECDEU Assessment Manual for Psychopharmacology. U. S. Department of Health, Education, and Welfare, Rockville, MD.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.

Hashemi, R., Morshedi, M., Asghari Jafarabadi, M., Altafi, D., Saeed Hosseini-Asl, S., Rafie-Arefhosseini, S., 2018. Anti-inflammatory effects of dietary vitamin D $_3$ in patients with multiple sclerosis. Neurology Genetics 4, e278. https://doi.org/10.1212/NXG.0000000000000278.

Hoffmann, M.R., Senior, P.A., Mager, D.R., 2015. Vitamin D supplementation and health-related quality of life: a systematic review of the literature. J. Acad. Nutr. Diet. 115, 406–418. https://doi.org/10.1016/j.jand.2014.10.023.

Israel, J.A., 2010. The impact of residual symptoms in major depression. Pharmaceuticals 3, 2426–2440. https://doi.org/10.3390/ph3082426.

Jorde, R., Kubiak, J., 2018. No improvement in depressive symptoms by vitamin D supplementation: results from a randomised controlled trial. J. Nutr. Sci. 7, e30. https://doi.org/10.1017/jns.2018.19.

Jorde, R., Sneve, M., Figenschau, Y., Svartberg, J., Waterloo, K., 2008. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. J. Intern. Med. 264, 599–609. https://doi.org/10.1111/j.1365-2796.2008.02008.x.

Khoraminya, N., Tehrani-Doost, M., Jazayeri, S., Hosseini, A., Djazayery, A., 2013. Therapeutic effects of vitamin D as adjunctive therapy to fluoxetine in patients with major depressive disorder. Aust. N. Z. J. Psychiatr. 47, 271–275. https://doi.org/10.1177/0004867412465022.

Kjærgaard, M., Waterloo, K., Wang, C.E.A., Almås, B., Figenschau, Y., Hutchinson, M.S., Svartberg, J., Jorde, R., 2012. Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: nested case-control study and randomised clinical trial. Br. J. Psychiatry 201, 360–368. https://doi.org/10.1192/bjp.bp.111.104349.

Krishnadas, R., Cavanagh, J., 2012. Depression: an inflammatory illness? J. Neurol. Neurosurg. Psychiatry 83, 495–502. https://doi.org/10.1136/jnnp-2011-301779.

Liu, W., Zhang, L., Xu, H.-J., Li, Y., Hu, C.-M., Yang, J.-Y., Sun, M.-Y., 2018. The anti-inflammatory effects of vitamin D in tumorigenesis. Int. J. Mol. Sci. 19, 2736. https://doi.org/10.3390/ijms19092736.

Lorenzetti, V., Allen, N.B., Fornito, A., Yücel, M., 2009. Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. J. Affect. Disord. 117, 1–17. https://doi.org/10.1016/j.jad.2008.11.021.

Mangin, M., Sinha, R., Fincher, K., 2014. Inflammation and vitamin D: the infection connection. Inflamm. Res. 63, 803–819. https://doi.org/10.1007/s00011-014-0755-z.

Martin-Vazquez, D.M.-J., 2016. Adherence to antidepressants: a review of the literature. Neuropsychiatry 6, 236–241. https://doi.org/10.4172/Neuropsychiatry.1000145.

Mauskopf, J.A., Simon, G.E., Kalsekar, A., Nimsch, C., Dunayevich, E., Cameron, A., 2009. Nonresponse, partial response, and failure to achieve remission: humanistic and cost burden in major depressive disorder. Depress. Anxiety 26, 83–97. https://doi.org/10.1002/da.20505.

Menon, V., Kar, S.K., Suthar, N., Nebhinani, N., 2020. Vitamin D and depression: a critical reappraisal of the evidence and future recommendations. Indian J. Psychol. Med. 42, 11–21. https://doi.org/10.4103/IJPSYM.IJPSYM_160_19.

Morisky, D.E., Green, L.W., Levine, D.M., 1986. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 24, 67–74. https://doi.org/10.1097/00005650-198601000-00007.

Moylan, S., Maes, M., Wray, N.R., Berk, M., 2013. The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. Mol. Psychiatr. 18, 595–606. https://doi.org/10.1038/mp.2012.33.

Mozaffari-Khosravi, H., Nabizade, L., Yassini-Ardakani, S.M., Hadinedoushan, H., Barzegar, K., 2013. The effect of 2 different single injections of high dose of vitamin D on improving the depression in depressed patients with vitamin D deficiency: a randomized clinical trial. J. Clin. Psychopharmacol. 33, 378–385. https://doi.org/10.1097/JCP.0b013e31828f619a.

Pan, A., Lu, L., Franco, O.H., Yu, Z., Li, H., Lin, X., 2009. Association between depressive symptoms and 25-hydroxyvitamin D in middle-aged and elderly Chinese. J. Affect. Disord. 118, 240–243. https://doi.org/10.1016/j.jad.2009.02.002.

Parker, G.B., Brotchie, H., Graham, R.K., 2017. Vitamin D and depression. J. Affect. Disord. 208, 56–61. https://doi.org/10.1016/j.jad.2016.08.082.

Penckofer, S., Kouba, J., Byrn, M., Ferrans, C.E., 2010. Vitamin D and depression: where is all the sunshine? Issues Ment. Health Nurs. 31, 385–393. https://doi.org/10.3109/01612840903437657.

Rapaport, M.H., Clary, C., Fayyad, R., Endicott, J., 2005. Quality-of-life impairment in depressive and anxiety disorders. Am. J. Psychiatr. 162, 1171–1178. https://doi.org/10.1176/appi.ajp.162.6.1171.

Rosen, C.J., Abrams, S.A., Aloia, J.F., Brannon, P.M., Clinton, S.K., Durazo-Arvizu, R.A., Gallagher, J.C., Gallo, R.L., Jones, G., Kovacs, C.S., Manson, J.E., Mayne, S.T., Ross, A.C., Shapses, S.A., Taylor, C.L., 2012. IOM committee members respond to Endocrine Society vitamin D guideline. J. Clin. Endocrinol. Metab. 97, 1146–1152. https://doi.org/10.1210/jc.2011-2218.

Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Stewart, J.W., Warden, D., Niederehe, G., Thase, M.E., Lavori, P.W., Lebowitz, B.D., McGrath, P.J., Rosenbaum, J.F., Sackeim, H.A., Kupfer, D.J., Luther, J., Fava, M., 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am. J. Psychiatr. 163, 1905–1917. https://doi.org/10.1176/ajp.2006.163.11.1905.

Schneider, B., Weber, B., Frensch, A., Stein, J., Fritz, J., 2000. Vitamin D in schizophrenia, major depression and alcoholism. J. Neural. Transm. 107, 839–842. https://doi.org/10.1007/s007020070063.

Sepehrmanesh, Z., Kolahdooz, F., Abedi, F., Mazroii, N., Assarian, A., Asemi, Z., Esmaillzadeh, A., 2016. Vitamin D supplementation affects the beck depression inventory, insulin resistance, and biomarkers of oxidative stress in patients with major depressive disorder: a randomized, controlled clinical trial. J. Nutr. 146, 243–248. https://doi.org/10.3945/jn.115.218883.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatr. 59 (Suppl. 20), 22–33 quiz 34-57.

Spedding, S., 2014. Vitamin D and depression: a systematic review and meta-analysis comparing studies with and without biological flaws. Nutrients 6, 1501–1518. https://doi.org/10.3390/nu6041501.

Vellekkatt, F., Menon, V., 2019. Efficacy of vitamin D supplementation in major depression: a meta-analysis of randomized controlled trials. J. Postgrad. Med. 65, 74–80. https://doi.org/10.4103/jpgm.JPGM_571_17.

Wang, Y., Liu, Y., Lian, Y., Li, N., Liu, H., Li, G., 2016. Efficacy of high-dose supplementation with oral vitamin D3 on depressive symptoms in dialysis patients with vitamin D3 insufficiency: a prospective, randomized, double-blind study. J. Clin. Psychopharmacol. 36, 229–235. https://doi.org/10.1097/JCP.0000000000000486.

White, J.H., 2012. Vitamin D metabolism and signaling in the immune system. Rev. Endocr. Metab. Disord. 13, 21–29. https://doi.org/10.1007/s11154-011-9195-z.

Yalamanchili, V., Gallagher, J.C., 2012. Treatment with hormone therapy and calcitriol did not affect depression in older postmenopausal women: no interaction with estrogen and vitamin D receptor genotype polymorphisms. Menopause 19, 697–703. https://doi.org/10.1097/gme.0b013e31823bcec5.

Zajecka, J., Kornstein, S.G., Blier, P., 2013. Residual symptoms in major depressive disorder: prevalence, effects, and management: (academic highlights). J. Clin. Psychiatr. 74, 407–414. https://doi.org/10.4088/JCP.12059ah1.

Zanetidou, S., Murri, M.B., Buffa, A., Malavolta, N., Anzivino, F., Bertakis, K., 2011. Vitamin D supplements in geriatric major depression. Int. J. Geriatr. Psychiatr. 26, 1209–1210. https://doi.org/10.1002/gps.2703.