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Research Paper

Vitamin D Supplementation in Chronic Schizophrenia Patients Treated with Clozapine: A Randomized, Double-Blind, Placebo-controlled Clinical Trial

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ABSTRACT

Background: While accumulating evidence suggests that vitamin D deficiency may be involved in the risk to develop schizophrenia and its outcome, there are no studies on vitamin D supplementation in this context. We sought to assess the effect of vitamin D supplementation on psychiatric, cognitive and metabolic parameters in chronic clozapine-treated schizophrenia patients.

Methods: This eight-week, randomized, double-blind, placebo-controlled clinical trial, recruited schizophrenia patients who had been maintained on clozapine treatment for at least 18 weeks and had low levels of vitamin D (<75 nmol/l) and total PANSS scores >70 (to ascertain the presence of residual symptoms). Patients were randomly allocated to either weekly oral drops of vitamin D (14,000 IU) or placebo and subsequently assessed at two-week intervals for psychosis severity, mood, cognition and metabolic profile.

Results: Twenty four patients were randomly assigned to vitamin D (aged 39.4 ± 9.6 years, 75% males) and the other 23 patients to the placebo arm (aged 42.5 ± 11.2 years, 60.9% males). After eight weeks, the vitamin D group exhibited a significant increase in vitamin D levels (31.4 vs −0.4 nmol/l, $p < 0.0001$). There was no significant effect of vitamin D on psychotic, depressive or metabolic parameters. However, in the vitamin D group, there was a trend towards improved cognition (effect size = 0.17, significance lost following Bonferroni correction).

Conclusions: Vitamin D supplementation was associated with a trend towards improved cognition, but did not affect psychosis, mood or metabolic status. It is possible that the robust decrease in the PANSS scores in both groups may have obscured an effect of vitamin D supplementation.

1. Introduction

Chronic schizophrenia patients maintained on clozapine represent the most difficult-to-treat portion of this population (Kane, 1996; Meltzer, 1997). Clozapine treatment is indicated for patients who do not respond sufficiently to numerous other antipsychotic treatments (Suzuki et al., 2011). Still, unfortunately, about 50% of patients receiving clozapine remain with significant residual symptoms despite attempts at optimization of treatment and augmentation with other psychotropic drugs (Buckley et al., 2001). Moreover, there is no consensus on effective augmentation of clozapine treatment (Lieberman and Stroup, 2011; Porcelli et al., 2011). Besides reducing psychotic burden, ameliorating cognitive impairments and negative symptoms is an important challenge for this population of schizophrenia patients. Impairment of executive functions and social cognition is one of the major disabilities in schizophrenia (Green and Harvey, 2014; McCleery et al., 2014).

The prevalence of physical health comorbidities is high in schizophrenia patients (Correll et al., 2017; De et al., 2011; Vancampfort et al., 2016) and consists mainly of metabolic syndrome(De et al., 2009c; Gardner-Sood et al., 2015; Vancampfort et al., 2015) that leads to a higher rate of cardiovascular morbidity(Correll et al., 2017;De et al.,

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2009a; Vancampfort et al., 2013). Cardio-metabolic complications are associated with significantly higher mortality rates and reduced life expectancy in the range of 15–20 years, compared to non-schizophrenia populations (De et al., 2009b; Hjorthoj et al., 2017; Nielsen et al., 2013). Recently it was shown that low vitamin D levels are associated with increased risk for metabolic syndrome and cardiovascular illness in schizophrenia patients (Lally et al., 2016).

The body content of 25 (OH) vitamin D is dependent on its synthesis in the skin by the enzyme 25-hydroxylase and its consumption in the diet. Increasing evidence suggests that vitamin D is important to brain development (Cui et al., 2013; Eyles et al., 2003; Groves et al., 2013). The vitamin D receptor and the enzyme 1-α-hydroxylase that is needed for the hydroxylation of the precursor molecule 25(OH) vitamin D to the active form, have widespread expression in the adult human brain (Eyles et al., 2013). Animal models of rats deprived of vitamin D in-utero showed enhanced spontaneous hyperlocomotion and increased activity on the elevated plus maze as well as impaired latent inhibition, which is a prominent feature of schizophrenia and attributable to impaired sensory gating and attentional deficits (Burne et al., 2014; Eyles et al., 2009). Epidemiological studies found ecological factors associated with increased risk for developing schizophrenia, such as latitude, urbanicity and dark skin tone, factors that are associated also with hypovitaminosis D (McGrath et al., 2010a). Previous studies also showed that low blood vitamin D levels during the first year of life increase the risk for psychosis in males (McGrath et al., 2010b). Additionally, infants who did not receive sufficient vitamin D supplements were also found to be at risk to develop psychosis later in adulthood (McGrath et al., 2004). Furthermore, several cross-sectional studies found high prevalence of vitamin D deficiency in schizophrenia patients (Boerman et al., 2016; Itzhaky et al., 2012) and two meta-analyses concluded that the vitamin D levels of schizophrenia patients tend to be low, compared to healthy controls (Belvederi et al., 2013; Valipour et al., 2014). Vitamin D deficiency has also been suggested to be associated with cognitive impairment in people with psychotic disorders (Nerhus et al., 2017).

However, the authors were unable to find any study that evaluated the direct effect of vitamin D supplementation on psychiatric, cognitive and metabolic status in schizophrenia patients and particularly in clozapine-treated patients. This is specifically important for this population since there are limited further treatment options for clozapine-treated patients with residual symptoms. We hypothesized that Vitamin D supplementation may serve as a relatively safe adjunctive treatment for schizophrenia patients with a partial response to clozapine. We assumed that increasing vitamin D levels in clozapine-treated chronic schizophrenia patients may lead to a corresponding improvement in their psychotic, cognitive, affective and metabolic parameters.

2. Materials and Methods

2.1. Participants

All inpatients and outpatients treated with clozapine during the period between 1.5.2014 and 30.9.2016 at Geha Mental Health Center (GMHC) were identified using the electronic medical record registry ($N = 174$). Potential participants were approached by the study nurse regarding participation in the study. The study was conducted according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (see CONSORT diagram – Fig. 1).

Patients who consented to participate were assessed for eligibility criteria which included: age between 18 and 65 years old, diagnosis of schizophrenia according to DSM-IV-TR criteria confirmed by two senior psychiatrists, treated with clozapine for at least 18 weeks and being on a stable clozapine dose for at least four weeks prior to enrollment, serum 25(OH) vitamin D level below 75 nmol/l (30 ng/ml) and total severity of psychopathology score, as measured by the Positive and Negative Symptom Scale (PANSS) total score above 70. This threshold was chosen to ascertain that the patients had sufficient residual symptoms to be optimized by vitamin D addition and to avoid a floor effect. Exclusion criteria included: learning disability, organic brain disease, parathyroid disorder, inborn/acquired vitamin D metabolism disorders and patients already treated with vitamin D supplementation. The sample size was calculated as 45, based on an effect size of 0.6 ($\alpha = 0.05$, power = 0.80) of the primary outcome measure (reduction in total PANSS score).

The study was approved by GMHC's institutional review board and is registered on ClinicalTrials.gov (NCT01759485). All participants

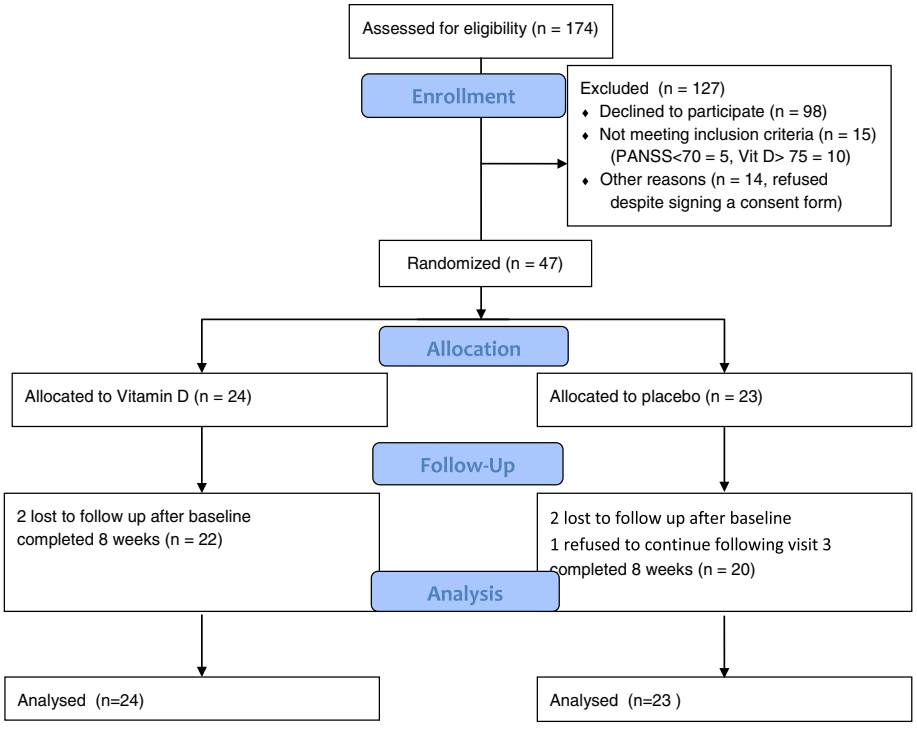

Fig. 1. CONSORT flow chart of the study recruitment and follow-up process.