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Research Paper

A molecular approach to treating cognition in schizophrenia by calcium channel blockade
An open-label pilot study of the calcium-channel antagonist isradipine

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ABSTRACT

Cognitive impairment is a prominent and difficult to treat symptom in schizophrenia (SZ), which is directly related to functional disability. A variant in the gene coding for the alpha 1C subunit of L-type voltage gated calcium channel (CACNA1C) has been shown to negatively affect several neurocognitive domains. We conducted a 4-week, open label, pilot study of isradipine, a calcium channel blocker, to determine its feasibility, safety, and efficacy in improving cognition in SZ patients.

Ten adults with stable SZ were started on a flexible dose of isradipine 5 mg/day (up to 10 mg/day) for 4 weeks. Weekly in-person visits tracked side effects and symptoms while neurocognition and functional capacity were assessed at baseline and week 4.

There were no serious adverse events reported. Newly emergent side effects were dizziness (1 new incidence at week 4); difficulty sleeping (2 new incidences at week 4); and decreased energy (3 new incidences at week 4). 1 patient discontinued medication and was withdrawn. Treatment did not exacerbate clinical symptoms. Although power is limited, results indicate no clear benefit on neurocognition but a positive effect (baseline mean = 6.8 ± 1.3 to week 4 mean = 7.9 ± 1.1; t = 2.91, p = 0.017) on functional capacity was noted.

This open label, pilot study provides preliminary evidence that isradipine is a relatively safe medication when used adjunctively in SZ patients. This study suggests that isradipine offers no clear cognitive and only minimal functional benefit; however, additional studies may be warranted in symptomatic patients, or those with specific CACNA1C genotypes.

1. Introduction

Cognitive impairment is a prominent and difficult to treat feature of schizophrenia (SZ) and is directly related to functional disability. The lack of progress toward novel and effective interventions is due, at least in part, to the fact that the underlying etiology of cognitive dysfunction in SZ is not known; however, convergent data support a neurodevelopmental model in which genetic factors play a significant role (Davis et al., 2017).

Genome-wide association studies (GWAS) have reached beyond the candidate gene level in very large samples and have identified several novel risk variants with high statistical confidence. Among the most widely studied of these is a variant in the gene coding for the alpha 1C subunit of the L-type voltage-gated calcium channel (CACNA1C) (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011). A single nucleotide polymorphism (SNP; rs1006737) in CACNA1C; initially associated with bipolar disorder (BD) (Ferreira et al., 2008; Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Sklar et al., 2008) has also been linked with SZ (Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013; Green et al., 2010; Hamshere et al., 2013; Nyegaard et al., 2010) and recurrent major depression (Green et al., 2010). More recently, large-scale GWAS studies (Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013; Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011) have reported transdiagnostic associations with multiple SNPs within CACNA1C, highlighting its unique convergence across disorders and underscoring its probably importance for understanding the brain as affected by neuropsychiatric

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Table 1
Literature on relationship between CACNA1C and cognition in BD and SZ.

Publication	Subjects	Cognitive tests	Results: *CACNA1C* & cognition	SNP, rs#
(Cosgrove et al., 2017)	157 healthy 557 broad psychosis 409 SZ/SZA	SWM (CANTAB) In replication studies: MATRICS working memory (Cardiff) N-back, DS (WAIS), SS (WAIS) (Germany)	- Associated with increased errors on CANTAB - Association in same direction within diagnostic groups (broad, narrow, HC), but was nonsignificant in HC - No association for verbal working memory - In replication analyses in two other samples: Cardiff (no association for working memory, but was associated with verbal memory), Germany (main effect for n-back, but not for digit/spatial span)	2007044
(Rolstad et al., 2016)	104 healthy 114 BD	TMT number sequencing (D-KEFS), Digit Symbol coding (WAIS-III), CDT, RCFT recall, DS (WAIS-III), LNS (WAIS-III), RCFT copy, BD (WAIS-III), Similarities (WAIS-III), Verbal Fluency Test (D-KEFS), Color-Word Interference (D-KEFS), Design Fluency (D-KEFS), Tower Test (D-KEFS), CPT	- No significant associations were found between CACNA1C and any cognitive domains or IQ	1006737
(Soeiro-de-Souza et al., 2013)	96 healthy 109 BD	LNS (WAIS-III), DS (WAIS-III), TMT, and WCST	- No influence of CACNA1C on cognition in HC	1006737
(Hori et al., 2012)	1132 healthy 552 SZ	Japanese versions of WMS-R, WAIS-R, and WCST	- Genotype was marginally significant for logical memory for SZ patients but not HC	1006737
(Zhang et al., 2012)	401 healthy 318 SZ 74 BP	Chinese versions of WAIS-R, N-back, DPX	- Healthy and SZ: Risk allele associated w impaired working memory (1-back, Bx condition of the DPX task)	1006737
(Thimm et al., 2011)	82 healthy	ANT	- Risk homozygotes impaired in Alerting and Orienting	1006737
(Krug et al., 2010)	63 healthy men	Semantic verbal fluency	- Risk carriers performed worse than non-carriers on semantic fluency tasks with abnormal activation patterns on fMRI	1006737
(Roussos et al., 2013)	530 healthy men	CANTAB	- No genotype effect on sensorimotor gating or CANTAB	1006737
(Erk et al., n.d.)	110 healthy	3 consecutive memory test (encoding, recall, and recognition),VIQ (MWT-B), -RAVLT	- Risk carriers exhibit reduction of ACC and bilateral hippocampal activation during episodic memory	1006737
(Bigos et al., 2010)	440 healthy 282 SZ	- Emotional memory, N-back	Risk carriers had increased activity in hippocampus during emotion processing and in PFC during N-back	1006737
(Splawski et al., 2005)	5 children	CELF, GFTA, NEPSY	- Timothy Syndrome with $Ca_V1.2$ missense mutation (G406R). - -All children showed developmental delays consistent with language, motor, and generalized cognitive impairment.	1006737

Key: HC = healthy controls, BD = bipolar disorder, SZ = schizophrenia, SZA = schizoaffective disorder, SWM = Spatial Working Memory, CANTAB = Cambridge Neuropsychological Test Automated Battery, MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia, DS = digit span, WAIS-III = Wechsler Adult Intelligence Scale version III, SS = spatial span, TMT = Trails Making Task, D-KEFS = Delis-Kaplan Executive Function System, CDT = Claeson-Dahl Test, RCFT = Rey Complex Figure Test, LNS = letter-number sequencing, BD = Block Design, CPT = Continuous Performance Test, WCST = Wisconsin Card Sorting Task, WMS-R = Wechsler Memory Scale-Revised, WAIS-R = Wechsler Adult Intelligence Scale-Revised, DPX = Dot Pattern expectancy, ANT = Attention Network Test, VIQ = Verbal Intelligence Quotient, MWT-B = Mehrfachwahl-Wortschatz-Intelligenztest, version B, RAVLT = Rey Auditory Learning Task, CELF = Clinical Evaluation of Language Fundamentals, GFTA = Goldman-Fristoe Test of Articulation, NEPSY = A Developmental Neuropsychological Assessment.

disturbance. Indeed, several subsequent studies have evaluated the effects of CACNA1C variation on neurocognitive capacity in healthy samples as well as in patients with SZ and bipolar disorder (BD); risk carriers evidence impairments in several cognitive domains. CACNA1C rs1006737 has been shown to affect neural networks underlying reward and emotional processing (Bigos et al., 2010; Wessa and Linke, 2009), verbal fluency (Krug et al., 2010), verbal memory (Cosgrove et al., 2017), alerting and orienting aspects of attention (Thimm et al., 2011), and executive functions (Bigos et al., 2010; Soeiro-de-Souza et al., 2013); however, not all studies have been positive (Hori et al., 2012; Rolstad et al., 2016). Table 1 summarizes the current literature (for recent review see Moon et al., 2018).

In addition to genetic evidence, peripheral and postmortem markers of calcium homeostasis have been found to be abnormal in patients with SZ, suggesting that calcium channel dysregulation may be a central feature of the disorder. Calcium channel blockers, and in particular dihydropyridines (DHPs) may serve to target this dysregulation. L-type channels are highly sensitive to DHPs, which, as a class, act to block the influx of Ca2+. DHPs have been widely used as anti-hypertensives, with more recent attention given to their potential to protect from neuronal damage associated with several pathological conditions (Hunter et al., 1997). Specifically, DHPs have been shown to block hippocampal (CA1) damage and to reduce memory impairment in animal models of hypoxia (Barhwal et al., 2009), diabetes (Tsukuda et al., 2008), cerebral ischemia (Iwasaki et al., 2007), and Parkinson's disease (Chan et al., 2007). Epidemiological data indicate that DHPs might prevent (Forette et al., 1998) or slow the progression of Alzheimer's disease (AD) in the general population (Fritze and Walden, 1995; Tollefson et al., 1998). Results from clinical trials however have been inconsistent (López-Arrieta and Birks, 2002); some agents do not cross the blood brain barrier (Anekonda et al., 2011) and some DHPs have shown benefits only for specific genotypes (Kennelly et al., 2011). In a high-throughput screening of candidate compounds for the treatment of dementia, which included several DHPs currently in clinical use (verapamil, diltiazem, nimodipine and isradipine), only isradipine provided a significant protective benefit and minimal toxicity at multiple levels of complexity (biochemical, cellular and whole organism), making it the most promising candidate in considering efforts to target brain-based phenotypes (Copenhaver et al., 2011).

Isradipine is a second-generation calcium channel blocker of the 1.4-dihydropyridine (DHP) class, which binds to both Cav1.2 and Cav1.3 channels. The Cav1.2 channel, which is specifically coded for by the CACNA1C gene, plays a critical role in hippocampal functioning and influences long term potentiation and spatial memory formation (Moosmang et al., 2005). Cav1.3 is encoded by CACNA1D and is primarily localized to the striatum (Tippens et al., 2008). Isradipine blocks Cav1.3 channel subtypes in dopamine (DA) cells in the substantia nigra (Chan et al., 2010) which is believed to be at least one of the its mechanisms of action resulting in neuroprotection in animal models of Parkinson's disease (PD) (Chan et al., 2010; Chang et al., 2010; Ritz et al., 2010). Isradipine has received some attention as a candidate for Alzheimer's Disease (AD) trials, due to data from animal models indicating its tolerability and superior blood-brain barrier penetrance, alongside its ability to attenuate beta amyloid toxicity, lower tau burden, and improve autophagy function in transgenic mouse models for AD (Anekonda et al., 2011). Isradipine has also been shown to protect against stroke (Lenhard et al., 2008) and ischemia (Campbell et al., 1997) in rat models of hypertension. Data from a pilot trial of isradipine in PD patients indicates safety and tolerability, with an optimal daily dose of 10 mg/day (Simuni et al., 2010).

We completed a four-week, open-label, pilot study of isradipine in a small sample (n = 10 completers) of symptomatically-stable patients with SZ. The primary goal of this pilot study was to assess the safety and feasibility of using isradipine in SZ. As a secondary aim, though underpowered to test in any definitive way, we investigated whether isradipine shows a positive signal for efficacy on the cognitive deficits in SZ.

2. Materials and methods

This study was reviewed and approved by the Institutional Review Board (IRB) at the Icahn School of Medicine at Mount Sinai. All patients signed an informed consent document before any study procedures were conducted.

This was an open-label study with a *flexible dosing schedule*, targeting an optimal dose of 10 mg/day (NCT01658150). Patients were screened and if deemed eligible, started on 5 mg/day at baseline and if tolerated, the dose was raised to 5 mg/BID with a total of 10 mg/day. The visit schedule included weekly in-person visits to track side effects and symptom ratings. Neurocognition and functional capacity were assessed by highly trained study staff at baseline and again at week 4 or end of study.

2.1. Patients

Patients were recruited through local advertisements in the New York City metropolitan area from January 2013 until August 2018. Inclusion criteria included age between 18 and 55; a diagnosis of schizophrenia or schizoaffective disorder as per the Structured Clinical Interview for the DSM-IV (SCID-IV); and symptom ratings indicating a residual phase of illness (Brief Psychiatric Rating Scale BPRS item scores of ≤4 on each of the following: hallucinatory behavior, unusual thought content, and conceptual disorganization, Hamilton Rating Scale for Depression HDRS total score < 12, and Clinician Administered Ratings Scale for Mania CARS-M total score < 5). Exclusion criteria were 1. History of CNS trauma, neurological disorder, attention deficit hyperactivity disorder (ADHD), mental retardation, learning disability, or other known non-schizophrenic cause of cognitive impairment; 2. DSM-IV diagnosis of substance abuse/dependence within 3 months or positive urine toxicology at screening that is not consistent with what participant reported; 3. pregnant women or women of child bearing potential who are not using a medically accepted means of contraception (including oral contraceptive or implant, condom, diaphragm, spermicide, intrauterine device, tubal ligation, or partner with vasectomy); 4. women who are breastfeeding; 5. active, unstable medical problem that may interfere with cognition; 6. current treatment for hypertension; 7. uncontrolled hypertension; 8. history of heart disease; 9. any drug known to interact with isradipine; 10. history of gastrointestinal strictures; 11. abnormal lab or electrocardiogram (ECG) at screen; and 12. significant suicidal ideation at baseline (HDRS item 3 > 2). Concomitant medications: Practical and ethical considerations prevent an exclusive focus on medication-free patients; however, we limited participation to individuals taking at least one and no > 2 concomitant antipsychotic medications and we excluded subjects who have received ECT within 12 months.

2.2. Measures

Safety was assessed weekly through clinician-administered and self-report measures, in addition to laboratory measures (blood pressure; heart rate; weight). An ECG was conducted at screening and at week 4. Symptom severity was rated at each visit using the Scale for the Assessment of Negative Symptoms (SANS), BPRS, and the HDRS. Cognition was assessed at baseline and at week 4 using the MATRICS Consensus Cognitive Battery (MCCB), which taps into seven domains of cognitive functioning including processing speed, attention/vigilance, working memory, verbal memory, visual memory, reasoning/problem solving, and social cognition (Nuechterlein et al., 2008). Alternate forms were utilized at the week 4 visit to reduce practice effects. Everyday functioning was assessed using the UCSD Performance Skills Assessment (UPSA) and Quality of Life Scale at baseline and week 4. Blood samples were collected at baseline for DNA extraction.

2.3. Statistical analyses

The results reported here are largely descriptive for safety and feasibility outcomes. To assess for efficacy on cognitive and functional outcome measures, we conducted paired-sample *t*-tests and calculated effect size changes using Cohen's d.

3. Results

This proof-of-concept trial focused on feasibility and safety as primary outcomes. Efficacy on cognition was secondary and is considered very preliminary.

3.1. Demographics

The sample consisted of 10 adults with a mean age of 38 ± 13.4 years, 7/10 were male, 7/10 were diagnosed with schizophrenia, and 3/10 were diagnosed with schizoaffective disorder. Race, based upon self-report, was distributed as follows: 6 Black, 2 Asian, 1 White, and 1 Mixed-race.

3.2. Feasibility

Recruitment was difficult, but this was not necessarily unexpected as inclusion/exclusion criteria for clinical trials are often limiting. In the case of this trial, we specifically had difficulty identifying eligible patients due to the exclusion of patients who were taking any cardiac/hypertensive medications. The second most common reason for exclusion was the high percentage of patients not currently taking a stable dose of psychotropic medications. Most of the patients that we screened via their enrollment in a larger non-intervention-based study (of > 100 patients who met diagnostic criteria) were ineligible due to these specific criteria. A total of 17 patients were consented to the study, with 6 screen fails. Screen fails were due to medication rule out, abnormal ECG, abnormal labs, positive urine toxicology, unwillingness to swallow pills, and scheduling complications (Supplemental Fig. 1).

3.3. Safety

There were *no serious adverse events* reported in the conduct of this trial. There was one patient who dropped out of the study after taking study drug for 3 days. This was a 33-year-old Hispanic female patient with schizophrenia who reported headache, flushing, and lightheadedness after 3 doses of 2.5 mg/day (she was taking half of the prescribed does of 5.0 mg/day). She discontinued medication and was withdrawn from the study. All of her labs/vitals/ECG were within normal limits and all reported AEs resolved by the time she was seen at a follow-up visit one week later.

Symptom severity measures were of interest in this trial primarily for safety assessment – to ensure that the study medication did not exacerbate psychosis, negative symptoms, or depression. Mean change for positive symptoms (BPRS) was −1.0 ± 2.5; negative symptoms (SANS) was −1.6 ± 3.3; and depressive symptoms (HDRS) was −0.6 ± 1.8. As all patients began the trial during a residual (non-acute) phase, no changes in symptom severity were of clinical concern for any patient. There were no cases of increased suicidality.

Blood pressure was closely monitored during the trial. At baseline, half of the patients (5/10) met strict criteria for hypertension (4 met Stage 1 criteria of > 130–139 diastolic or > 80–89 and 1 met Stage 2 criteria). At week 4, only 2 patients continued to be hypertensive (3 cases improved) and no new incidences were noted. The mean change in weight over the 4-week study was −0.16 (± 4.1) pounds; however, there was a significant range in weight change (one patient lost 8 lbs., and another gained 5.6 lbs.).

Other common adverse events were assessed by direct query by the study physician at each visit. Details are shown in Table 2. The only newly emergent side effects (change since baseline report) that were reported were dizziness (1 new incidence at week 4); difficulty sleeping (2 new incidences at week 4); and decreased energy (3 new incidences at week 4, 2 of which reported difficulty sleeping as well). As this was an open-label study, we are unable to compare the frequency of these new reports with a placebo group.

3.4. Cognitive and functional outcomes

This was an open-label pilot study which is inherently underpowered to truly test for clinical efficacy; however, the goal was to assay systematic signals (both positive and negative effects) on cognition and functional capacity.

Preliminary evaluation of the data indicates *no clear benefit on any measured aspect of cognition*. When comparing baseline performance on the MCCB composite with performance at week 4, we see non-significant improvement as a group ($t = 0.77$, $df = 9$, $p = 0.46$). Similar non-significant changes were noted across all MCCB domains (Table 3). There was some variability/heterogeneity in cognitive response which is depicted at the individual patient level in Fig. 1; however, given the small sample, we are unable to determine any clear predictors of outcome.

Of note, our functional capacity measure, the UPSA communication score did improve significantly overall (baseline mean = 6.8 ± 1.3 to week 4 mean = 7.9 ± 1.1; $t = 2.91$, $p = 0.017$). This is a large effect size (Cohen's $d = 0.91$) with a more consistent pattern of improvement across subjects (Fig. 2). A recent study estimated practice effects in SZ patients administered the UPSA to be considerably smaller (Cohen's $d = 0.35$) than the change that we are reporting here (Keefe et al., 2016). Nonetheless, given the lack of corroborating improvement on other measures of cognition and the preliminary nature of this study, it is unknown whether these gains represent clinically-meaningful change.

4. Discussion

This open-label pilot study provides preliminary evidence that isradipine is relatively safe when used adjunctively in patients with schizophrenia (SZ), as no serious adverse events were noted. Common side effects were minimal. By design, this study cannot determine whether the agent might be useful in treating positive or negative symptoms of the illness, as patients were very stable at the time of entry; however, there were no cases of clinical exacerbation after 4-weeks of treatment with isradipine. Mild hypertension that was present in 5 patients at baseline was normalized by week 4 in 3 of these cases.

The primary domain of interest for efficacy was cognition – and the study was quite convincingly negative on this outcome. These data, although very preliminary, may suggest that blocking the influx of calcium, at least with isradipine, is unlikely to produce a pronounced cognitive benefit in SZ. We did find a positive change on the UPSA, indicating some improvement in functional capacity; however, this result should be interpreted with caution given the preliminary and open-label nature of this trial.

The physiological effects of isradipine are fairly well understood, with broad effects on both long-term potentiation and dopaminergic tone in subcortical areas. These effects are among the reasons that we hypothesized that isradipine might influence cognitive functioning; however, given the lack of improvement on cognitive measures in our study, it is more difficult to speculate how isradipine's physiological effects would influence functional capacity. Thus, the most parsimonious explanation is that these effects may be a consequence of isradipine's effects on hypertension. There are several lines of evidence that would support this explanation, including a recent study (de Heus et al., 2019) which showed that elevated day-to-day variability in blood pressure was associated with greater cognitive and functional decline in patients with Alzheimer's disease. While SZ is not always considered to

Table 2
Adverse events: Baseline vs. week 4 (end of study).

Queried adverse events (AE)	Baseline (# reporting/10)	Week 4 (# reporting/10)	Note
Diarrhea	0	0	–
Constipation	0	0	–
Dry Mouth	0	0	–
Nausea	1	0	Resolved since baseline
Palpitations	0	0	–
Dizziness	0	1	New since baseline
Chest Pain	0	0	–
Rash	0	0	–
Perspiration	0	0	–
Itching	0	0	–
Dry skin	1	0	Resolved since baseline
Headache	0	0	–
Tremors	0	0	–
Poor coordination	1	0	Resolved since baseline
Blurred vision	1	0	Resolved since baseline
Tinnitus	2	1	No change from baseline
Difficulty urinating	0	0	–
Painful urination	0	0	–
Frequent urination	2	1	No change from baseline
Menstrual irregular	3	3	No change from baseline
Difficulty sleeping	1	3	Two new since baseline
Hypersomnia	1	0	Resolved since baseline
Loss of libido	1	0	Resolved since baseline
Anxiety	2	2	No change from baseline
Poor concentration	2	1	New since baseline
Malaise	0	0	–
Restlessness	1	1	No change from baseline
Fatigue	2	1	No change from baseline
Decreased energy	0	3	Three new since baseline

Table 3
Changes in neurocognitive domains: Baseline vs. week 4 (end of study).

Domain	Baseline (n = 10)		Week 4 (n = 10)		t	p
	Mean	SD	Mean	SD		
Speed of processing	44.9	9.36	44.7	10.28	0.08	0.94
Attention/vigilance	39.2	10.80	39.5	11.29	−0.08	0.94
Working memory	40.1	13.46	40.5	13.87	−0.16	0.88
Verbal learning	44.4	9.61	39.3	4.11	1.69	0.13
Visual learning	48.9	14.06	50.5	10.97	−0.51	0.62
Reasoning and problem solving	48.2	13.88	44.0	10.24	1.83	0.10
Social cognition	40.4	9.47	41.0	11.84	−0.23	0.82
Overall composite	39.7	13.33	38.2	12.56	0.77	0.46

be a degenerative condition (aside from early definitions), it has a very high rate of stable cognitive impairment. Perhaps not uncoincidentally, schizophrenia also has high medical comorbidity and hypertension is common (Howell et al., 2019). In our study, our patients were symptomatically stable, but half of the patients met strict criteria for hypertension at baseline. Most of these patients showed significant stabilization of blood pressure by week 4, which could be a potential explanation for functional improvement in the absence of changes in symptom severity or cognitive impairment. Indeed, prior work has suggested that both psychiatric symptoms and physical functioning are major determinants of subjective disability in both patients with schizophrenia and bipolar disorder (Strassnig et al., 2018) and a recent meta-analysis demonstrates a consistent relationship between hypertension and cognitive and functional impairment in schizophrenia (Bora et al., 2017).

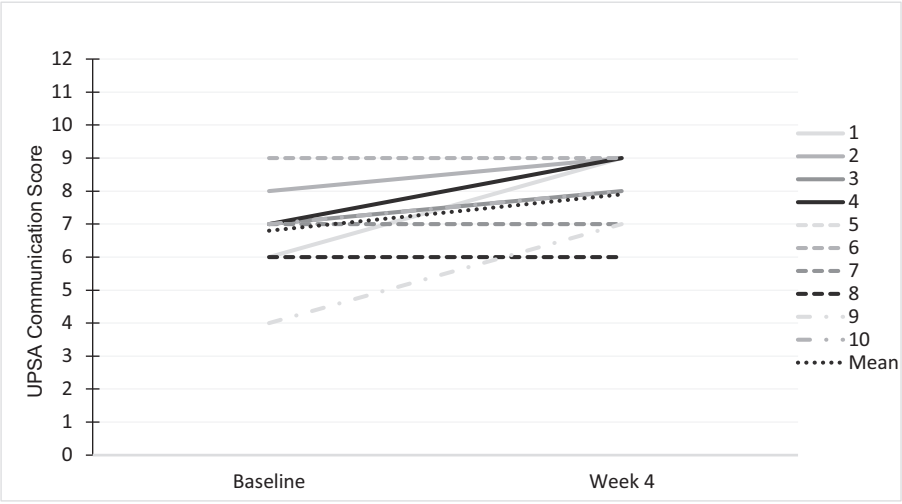

Fig. 1. Variability in UPSA Communication Score, depicted at the individual patient level.

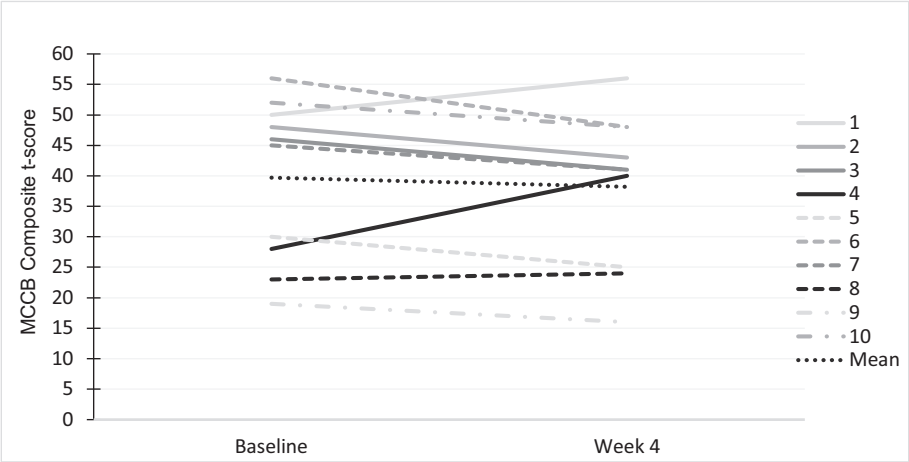

Fig. 2. Variability in MCCB composite t-score (mean = 50 SD = 10, with higher scores indicating better performance), depicted at the individual patient level.

Prior studies of Ca2+ channel blockers in affective and substance disorders (Casamassima et al., 2010) are mixed and depend upon outcome measure (depression, mania, cycling, relapse) and the pharmacodynamics of the specific agent or class of agent utilized [e.g. verapamil (a phenylalkylamine), isradipine, nimodipine (DHPs)]. A pilot study of isradipine in depressed patients with bipolar disorder provides early evidence of a potential anti-depressant effect of this agent, but sample size was small and there were no measures of cognition or functioning reported (Ostacher et al., 2014). Of relevance to our work, Krupitsky et al. (2001) conducted a double-blind, placebo-controlled trial of nimodipine in 26 alcohol-dependent men as a pre-treatment to ketamine, an NMDA receptor antagonist which can produce SZ-like syndromes including psychosis, negative symptoms, and cognitive impairment in healthy humans. Nimodipine pre-treatment significantly attenuated the effects of ketamine with regard to psychosis, negative symptoms, dysphoria, verbal fluency impairment and learning deficits. In fact, nimodipine not only reduced the capacity of ketamine to induce memory deficits but actually improved memory performance in this cohort. These results alongside convergent evidence that calcium channel dysfunction represents a core pathogenic feature in SZ, support continued evaluation of DHPs, in general, in neuropsychiatric disorders.

Our study had several limitations including its open-label design and the small sample size. Although we only had a total of 10 completers, there was no compelling evidence of any positive cognitive effects in the first ten participants and the risk of exposing additional subjects to an experimental drug was deemed to outweigh the benefits of continuing to enroll for the sake of statistical power. In addition, the decision to focus on stable patients in the residual phase was done to reduce the chances of pseudospecificity and to isolate potential effects on neurocognition. This design did not allow us to test the effects of isradipine on clinical symptoms of SZ.

Despite the negative outcome, this was a proof of concept study that provides important early data on safety and feasibility of using isradipine in patients with SZ. There remains a possibility that the heterogeneity in cognitive response that was noted may be related to genetic variation in the *CACNA1C* gene. Given the small sample, we do not anticipate any measurable main effects of genotype, but a genotype-specific response remains a plausible, testable hypothesis – which could inform whether future studies stratified by genotype may be warranted.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scog.2020.100180.

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CRediT authorship contribution statement

Katherine E. Burdick: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Mercedes Perez-Rodriguez:** Data curation, Supervision. **Rebecca Birnbaum:** Data curation, Supervision, Writing - review & editing, Writing - original draft. **Megan Shanahan:** Data curation, Supervision. **Emmett Larsen:** Data curation. **Cierra Harper:** Writing - review & editing, Writing - original draft. **Jessica Poskus:** Writing - review & editing, Writing - original draft. **Pamela Sklar:** Conceptualization.

Declaration of competing interest

None.

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