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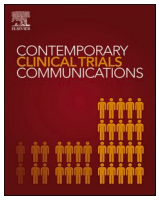

# Adjunctive methylphenidate extended release in patients with schizophrenia: Protocol of a single-centre fixed dose cross-over open-label trial to improve functional and cognitive outcomes

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ABSTRACT

*Background:* Cognitive symptoms, among the core symptoms of schizophrenia, are associated with poor functional outcome and burden of illness. To date, there is no effective pharmacological treatment for these symptom clusters. Augmentation with psychostimulants has been proposed as a potential treatment option.
*Objectives:* The present study aims to assess off-label use of adjunctive methylphenidate extended release (ER) in patients with schizophrenia who are stable on antipsychotic medications, and to assess its efficacy on functioning and cognitive outcome.
*Methods:* This is a single centre study at the Royal Ottawa Mental Health Centre. An open-label fixed dose controlled cross-over trial is planned. Eligible participants will be randomized into one of two arms of the study: 1) four weeks of add-on methylphenidate ER 36 mg, or 2) four weeks of treatment as usual. At 4 weeks, participants will switch arms. The duration of the study includes 8 weeks of treatment and a follow-up visit at 12 weeks. Primary outcome measures include tablet-based tests of functioning and cognition (VRFCAT and BAC) and will be administered at baseline and every 4 weeks. We are aiming to recruit a total of 24 participants.
*Expected outcomes:* The proposed project intends to assess a potential treatment option for cognitive deficits of schizophrenia, for which there are no recommendations by current treatment guidelines. The novelty and significance of the current study is that it investigates this intervention and assess applicability of it in a "real world setting" in a tertiary care hospital.

## 1. Introduction

Of the major features of schizophrenia spectrum illness, cognitive symptoms have been associated with poor functional outcome and burden of illness [1]. Cognitive symptoms include a broad array of deficits such as problems with working and verbal memory, attention, processing speed and executive function [2]. Treatment with conventional antipsychotics, including first and second generations, is reasonably effective for positive symptoms in adherent patients, however, the efficacy of antipsychotics with respect to cognitive symptoms ranges from minimal to modest at best [3,4]. Numerous pharmacological augmentation strategies have been studied for the treatment of cognitive symptoms with varying degrees of success. Nonetheless, to date there is no effective pharmacological treatment for these symptom clusters [5] and psychosocial approaches have major limitations. Cognitive remediation is a psychosocial intervention for treatment of cognitive symptoms in schizophrenia. Although, this treatment approach has shown positive results in randomized controlled trials [6], the effectiveness remain unclear to date in "real world" schizophrenia [7] and accessibility remains a clinical challenge [8]. In general, psychosocial interventions (including but not limited to cognitive remediation) remain poorly available to clinical populations with schizophrenia in the

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Western world: for instance, in 2010, only 15 % of the 6007 participants with schizophrenia in the ESPASS cohort had access to any psychosocial intervention [9]. Other emerging non-pharmacological Tx include aerobic exercise in treatment of cognitive deficits in schizophrenia [10].

Among the pathophysiological hypotheses for schizophrenia, is the imbalance between cortical and subcortical dopamine systems: dopaminergic hyperactivity in subcortical regions is implicated in the pathophysiology of positive symptoms [11] and hypoactivity in the pre-frontal cortex and mesocortical pathways has been associated with negative and cognitive symptoms [12]. It is noteworthy that although the dopamine hypothesis of schizophrenia is among one of the most enduring ideas in psychiatry, it has many limitations [13] and there is accumulating evidence pointing to the involvement of other neurotransmitters in addition to dopamine [14]. Nonetheless, given the proposed role of dopaminergic hypoactivity, augmentation with psychostimulants has been postulated as one of the potential treatment options for cognitive symptoms of schizophrenia [5]. However, the major drawback for use of these agents is a potential risk of relapse or worsening of psychosis through direct or indirect dopamine agonism activity and a great deal of caution has been called for in the use of stimulants in individuals with psychosis [15]. Other potential issues that arise with the use of psychostimulants in patients with psychosis include concerns regarding development of tolerance [16], rebound effect following discontinuation [5] and the potential for induction of super-sensitivity psychosis [17].

The preliminary results of earlier studies indicated improvement of negative symptoms with off-label use of adjunctive psychostimulants [18–20]; however, the use of psychostimulants has gradually faded in the schizophrenia literature considering the potential psychogenic role of these agents in this patient population [21]. A more recent open-label trial showed significant improvement of negative symptoms at week 10 with adjunctive lisdexamfetamine in stable patients with schizophrenia, who had prominent negative symptoms [22]. A randomized double-blind controlled trial of 31 participants, focusing on safety and pharmacokinetics of lisdexamfetamine, showed no significant change in negative symptoms but there was improvement in a measure of executive function and visual learning [23]. To our knowledge, these two studies are the only available studies on subacute use of psychostimulants in schizophrenia. Both studies reported safe use of psychostimulants in stable patients with schizophrenia and had no cases with worsening of neuropsychiatric symptoms [22,23].

A recent systematic review by Solmi et al. (2018) [5] did not find any evidence for efficacy of psychostimulants for negative symptoms. They reported potential improvement of cognitive symptoms with adjunctive psychostimulants. However, the majority of studies in this review were psychostimulant challenge design (i.e., acute administration of a single or few doses) and the review also included studies of non-dopaminergic stimulants (i.e modafinil). Unsurprisingly, participants of psychostimulant trials were carefully selected, and almost no studies included those with prominent positive symptoms [5]. Nonetheless, the evidence remains inconclusive regarding adjunctive use of psychostimulants in schizophrenia.

### 1.1. Preliminary data

In our retrospective chart review study [24] at the Royal Ottawa Mental Health Centre, approximately 6 % (77/1300) of outpatients with schizophrenia were prescribed psychostimulants by their treating psychiatrists. The results of our study showed chart based evidence of significant improvement among 42.2 %, of whom the majority (62 %) had improvement in cognitive symptoms. An additional 27.7 % showed minor improvement. Our results also showed chart review evidence of worsening or emergence of psychosis at varying degrees among 1/3 of participants. Worsening or emergence of psychosis was defined as worsening of symptoms requiring medication adjustment (and/or admission). Of the factors assessed, dose of the psychostimulant was the only factor associated with worsening or relapse. Doses of maximum or above were significantly associated with risk of worsening or emergence psychosis; whereas medium or low doses were not associated with worsening of psychosis. Our retrospective study showed a significantly higher rate of relapse compared to other studies [22], likely due to factors such as use of higher doses of psychostimulants and lack of stringent selection criteria. In this study, we will mitigate the identified risks, aiming to use methylphenidate extended release (ER) at a low dose (36 mg) in the controlled inpatient setting of the Recovery Program of the Royal Ottawa Mental Health Centre (please refer to section 3.3 "Safety Considerations" for further details). The present study aims to assess off-label use of adjunctive methylphenidate ER in patients with schizophrenia who are stable on antipsychotic medications, and to assess its efficacy on functioning and cognitive outcome.

## 2. Objectives and hypothesis

This project focuses on assessing efficacy of off-label use of adjunctive methylphenidate ER 36 mg among 24 stable patients with schizophrenia spectrum illness, while monitoring for safety.

The primary objective is.

1) To evaluate the impact of treatment with adjunctive methylphenidate ER 36 mg on functioning, using the Virtual Reality Functional Capacity Assessment (VRFCAT).

We hypothesized:

Adjunctive methylphenidate ER 36 mg improves functional outcome in patients with schizophrenia, who are admitted to the inpatient Recovery Program.

The secondary objective is.

1) To assess the efficacy of adjunctive methylphenidate ER 36 mg, in comparison to treatment as usual, on cognitive deficits in 24 stable patients with schizophrenia, using the Brief Assessment of Cognition (BAC).

## 3. Trial design

Trial registration: ClinicalTrials.gov, NCT05414058. Registered June 10, 2022. https://www.clinicaltrials.gov/ct2/show/NCT05414058.

### 3.1. Randomized controlled trial (RCT) design overview

This is a single centre study at the Royal Ottawa Mental Health Centre, Ottawa, Canada. An open-label fixed dose controlled cross-over trial is planned. Individuals with schizophrenia who are stable on any anti-psychotic medications will be invited to participate in the study. Participants will be randomized into one of two arms: 1) participants will receive four weeks of add-on methylphenidate ER 36 mg, or 2) participants will receive 4 weeks of treatment as usual (no-treatment control group). At 4 weeks, participants will switch arms for another 4 weeks. As such, those who initially received treatment as usual will receive methylphenidate ER 36 mg and those who were assigned to add-on methylphenidate ER will continue with treatment as usual. The cross-over design allows for the control of confounding factors. The duration of the study is 12 weeks for each participant, including 8 weeks of treatment (4 weeks treatment as usual and 4 weeks treatment as usual + adjunctive methylphenidate ER) and a follow-up visit at 12 weeks (end of study).

A number of standardized scales will be used to measure functional capacity (VRFCAT), cognition (BAC) and symptom severity (PANSS-6). Scales will be administered at baseline, at regular intervals during the 8 week period of the RCT and at follow up. The scales will be used for comparison analysis between active and control treatment arms. We are aiming to recruit a total of 24 participants.

#### 3.1.1. Randomization

All patients who meet eligibility criteria and consent to participate in this trial will be informed that they will receive treatment as usual followed by methylphenidate ER or the reverse order of treatment. Patients will be randomized to either one of the treatment orders. Patients' initials and identification number will be given to the project coordinator who will conduct the randomization, using Research Randomizer [25] (computer software).

#### 3.1.2. Investigational product accountability

The Pharmacy at the Royal Ottawa Mental Health Centre will be responsible for ordering, storage and delivery of the product. For inpatients, the Pharmacy will dispense the medication to Omnicell per a supply of 7 days. Medications will be administered daily to participants by unit nurses and will be recorded in patients' electronic medical record as per required reporting practices. For outpatients, the Pharmacy will dispense the medication directly to the patient per a supply of 7 days.

### 3.2. Selection and withdrawal of participants

#### 3.2.1. Sample size and population

A total of twenty four participants will be enrolled from the Schizophrenia Program at the Royal Ottawa Mental Health Centre. Participants will be recruited from theinpatient (north, south and Recovery) and outpatient units of the Schizophrenia Recovery Program (our outpatient program currently has approximately 1500 registered patients). Inpatients from the north/south units would meet the eligibility criteria close to discharge or while waiting for housing. Our inpatient unit is a long-term stay, and at times patients will stay several months following stabilization pending housing situation. The inpatient participants who enroll in the study will complete the study during their stay and prior to discharge. The north and south inpatient units consist of 46 beds. The inpatient Recovery Program is a 24-bed unit that aims to support patients with schizophrenia achieve their recovery goals such as improving basic skills related to independent living as well as vocational and educational goals.

#### 3.2.2. Referral requirement

Recruitment will be through referrals from treating psychiatrists who will assess that the following criteria are met.

- Current inpatient or outpatient of the Schizophrenia Recovery Program of the Royal Ottawa Mental Health Centre
- Between the ages of 18 and 55
- Has schizophrenia spectrum illness based on DSM-5 criteria (please specify)
  - ☐ Schizophrenia
  - ☐ Schizoaffective Disorder
- Patient is stable on any antipsychotic medication
- Patient has been clinically stable for at least 4 weeks prior to referral including:
  - ☐No clinically significant change in symptoms
  - ☐No addition/removal of antipsychotic, or change in antipsychotic dosage (>20 %)
  - ☐No psychiatric admission for an acute episode
- No ECT treatment in past 6 months
- No history of traumatic brain injury
- No contraindication to psychostimulant (ie uncontrolled hypertension, significant cardiovascular abnormality, known history of glaucoma)
- No known family history of premature cardiac death (for males <45, females <55)
- No diagnosis of substance induced psychosis
- No diagnosis of neurodevelopmental delay, intellectual disability, or neurocognitive disorder (dementia)
- No diagnosis of another currently significant and unstable psychiatric condition (e.g. depressive episode, active substance use disorder)
- No history of previous safety concerns directly driven by positive symptoms (e.g history of suicide attempt as directed by auditory hallucinations)
- No current active suicidality

#### 3.2.3. Informed consent

A written informed consent will be obtained if participants choose to enroll in the study. Participants and their SDMs (when applicable) will be informed that they can withdraw consent at any time during the study. They will also be informed that their consent is an ongoing requirement over the course of the study, and that they can ask questions at any time.

#### 3.2.4. Eligibility

Once informed consent has been obtained, patients will be seen for an initial assessment to determine eligibility. The following inclusion and exclusion criteria will be used.

➢ *Inclusion criteria:*

1. Patient from the Schizophrenia Recovery Inpatient or Outpatient Units
2. Adult between the ages of 18–55; we chose an upper age limit of 55 years to exclude patients with potential age-related cognitive impairments which usually occur about a decade earlier in patients with schizophrenia
3. Patients with schizophrenia spectrum illness, on any antipsychotic medication
4. Clinically stable for the past 4 weeks (see above for details)
5. Patients who have decisional capacity to give consent, and those who do not have decisional capacity to give consent (requiring a substitute decision maker)
6. Able to communicate in English
7. Women of childbearing potential will be asked to use a reliable method of contraception

➢ *Exclusion criteria:*

Participants will be excluded if they.

1. Have known sensitivity to methylphenidate ER, as documented in the electronic medical record OR, as reported by the patient AND verified by pharmacy
2. Currently on receiving treatment with any psychostimulant medication
3. Have had treatment with ECT in the past 6 months
4. Have a documented history of traumatic brain injury
5. Have a contraindication to psychostimulants including:
   a. Uncontrolled hypertension
   b. Significant cardiovascular abnormality including history of cardiac interventions, history of myocardial infarction, unstable arrhythmia, congenital heart disease
   c. Known family history of premature cardiac death (for males <45, females <55)
   d. Known history of glaucoma
6. Are currently pregnant or planning to become pregnant-a rapid urine pregnancy test will be done for female participants, and a refusal to take the test or a positive test will exclude the participant
7. Have a diagnosis of substance induced psychosis
8. Have any of the following diagnoses: neurodevelopmental delay, intellectual disability, or neurocognitive disorder (dementia)
9. Have a diagnosis of another currently significant and unstable psychiatric condition (i.e. depressive episode, active substance use disorder, etc.)

10. Have a history of previous safety concerns directly driven by positive symptoms (e.g history of suicide attempt as directed by auditory hallucinations)
11. Have current active suicidality

Inclusion and exclusion criteria will be determined based on Physician report and review of the EMR.

#### 3.2.5. Enrolment

Following the determination of eligibility, at t0, demographic data (age, sex, relationship status and source of income) and relevant medical information will be recorded using our investigator-created Patient Information Questionnaire. Participants will be asked to complete a Diversity Questionnaire. A medical history and physical exam will be done using the Canadian ADHD Resource Centre Alliance (CADDRA) form for history and physical exam prior to initiation of psychostimulants. Medical information includes psychiatric and medical diagnoses, number of previous episodes/admissions, duration of illness, age at onset and current medications. Following the completion of treatment, information from the outcome measures will be recorded on the Data Collection Form created by investigators. Weight, blood pressure and pulse will be measured.

Participants will then be randomized with a 1:1 ratio into one of two arms: 1) starts with active treatment and 2) starts with treatment as usual, using a computer generated sequence. Participants will switch over group assignments after 4 weeks.

#### 3.2.6. Participant's withdrawal/dropout

Patients and, when applicable, their substitute decision makers (SDMs) may opt to withdraw consent at any time during the study, for any reason. During the study period, patients will continue to receive care from their psychiatrists as usual. A decision for early discontinuation of the intervention can be made based on clinical need of the patient including acute need for psychiatric medication adjustment, exacerbation of psychosis or development of intolerable side effects. The trial will be terminated for patients who require a switch to another antipsychotic or those who undergo a major dose increase (>20 % of the dose they were on at baseline).

Participants who withdraw will have the option to withdraw their data, if they choose to. Participants who choose to withdraw from the treatment will stop receiving the study medication (methylphenidate ER). No tapering dose is required for psychostimulants. Participants who are withdrawn from the study will be offered follow up at 4 weeks post study-withdrawal, similar to other participants. However, they may choose no follow up with the research team and may opt to have follow up with their treatment team.

### 3.3. Treatment of participants

➢ *Apo-Methylphenidate ER,* 36 mg*, oral, once a day, every morning*

For the purpose of this study, we chose methylphenidate ER considering it is the most commonly used slow release psychostimulant. Methylphenidate exerts classic stimulant effect in the prefrontal cortex by increasing the concentration of dopamine and norepinephrine (NE) in presynaptic neurons, through blocking their reuptake. More specifically, it inhibits the transporters of these neurotransmitters, increasing the concentration of dopamine and NE in the synaptic cleft [26]. It has a 3.5 h half-life, reaches an initial maximum plasma concentration at about 1 h followed by gradual ascending concentration over the next 5–9 h. Methylphenidate ER tablets will be taken orally by participants, once a day. It will be started at 18 mg to test tolerability and will be titrated at day 7 to a dose of 36 mg. The maximum dose of methylphenidate ER in adults is 108 mg [27]. However, we chose 36 mg for the purpose of this study, considering that the risk of side effects with a stimulant is dose dependent and as such, the potential risk for worsening of psychosis at higher doses.

Patients will continue their regular medications as per standard of care. No dose adjustment is required if a patient misses 1–2 doses (or more) of the medication.

➢ *Treatment as usual*

Participants in the treatment as usual arm will continue with their current treatment as decided by their treatment team.

This study does not incorporate a washout period due to the short half-life of 3.5 h for the medication. For the purpose of this study, we opted not to use a placebo due to feasibility limitations. Our pharmacy does not have the capacity to produce identical placebo tablets or capsules and also, we were unable to access identical placebo through pharmaceutical companies. However, considering the limitations and the pilot nature of our study, our current study design could be adequate in answering our study questions on the effectiveness and safety of the study medication as a pilot trial. Acknowledging the lack of placebo and blinding remain as the limitations, we do not anticipate a significant impact on performance of participants, for the following reasons.

1) Our outcome measures assess cognition and functional capacity of participants, which are not expected to be impacted by awareness of the study allocation (i.e patients' knowledge of taking stimulants or not cannot influence how they perform on cognitive/functional testing) [28,29].
2) Our outcome measures are tablet-based computerized assessments. As such, raters (blinded or unblinded) could not impact the outcome.

#### 3.3.1. Monitoring of participants during the study period

Participants will be asked to participate in a weekly visit with the research assistant during the 8 weeks of the trial and one visit at week 12 for follow up. In each weekly visit, participants will be asked questions about their experience with the study medication and potential experience of side effects using the checklist from the CADDRA Patient ADHD Medication Form, that is specifically designed for monitoring side effects of psychostimulants by Canadian guidelines. Patients' medical records will be reviewed to ensure medication compliance. They will have their weight, blood pressure and pulse rate checked during the weekly visits. Participants are also instructed to contact the research team, if they have any concerns.

#### 3.3.2. Psychiatric follow up during the study period

During the study period, patients will continue their routine care and follow ups with their treating psychiatrist and treatment team. Concomitant medications that were part of the patients' pharmacotherapy prior to the study will be kept at the same dose. During the trial, benzodiazepines, zopiclone, and melatonin at clinically indicated doses will be allowed for treating any sleeping difficulties or anxiety symptoms that emerge. The dose adjustment of these psychotropic medications will be at the discretion of the treating psychiatrist. We will track the use of benzodiazepines, zoplicone and melatonin and any dose changes in our participants and will control for these variables in our analysis.

#### 3.3.3. Safety consideration

To mitigate the risk for potential exacerbation of psychosis, a number of precautions have been considered. First of all, this study uses a low dose of methylphenidate ER. Our study uses a dose of methylphenidate ER (36 mg) which is a low dose in adults, considering the maximum dose of 108 mg. Like other psychostimulants, side effects are dose dependent.

Our retrospective published chart review study [24] showed significant association with use of higher doses and risk of worsening of psychosis. There was no significant relationship with medium (54 mg) or low doses (36 mg or less) and as such, the choice of a low dose in this study is to mitigate the identified risk. Secondly, this study will be conducted in stable patients that are closely followed and monitored by a treatment team and can access timely intervention before they experience significant worsening. In a report on 100 patients with schizophrenia who are treated with antipsychotic medications, authors reported no adverse acute, subacute, or long-term consequences from the Experimental Medicine use of amphetamine [30]. Psychostimulants are usually well-tolerated, with the most reported side effects being reduced appetite and a slight delay in falling sleep. Side effects of stimulants are dose-dependent, and are generally mild to moderate in most patients. Common adverse effects of stimulants include insomnia, anorexia, nausea, decreased appetite, weight loss, headache, increased blood pressure, elevated pulse, abdominal pain, and irritability [31].

### 3.4. Outcome measures

The time points for assessments will be as follows: 1) t0: baseline, 2) t1: at 4 weeks, 3) t2: at 8 weeks, 4) t3: at 12 weeks (follow up). Assessments will be done within ±2 days of the time point. Please refer to Table 1 for details around each of the study visits.

Primary outcome variable, defined as improvement in functioning and will be measured using the Virtual Reality Functional Capacity Assessment (VRFCAT) tool. VRFCAT will be implemented at t0, t1, and t2.

➢ The Virtual Reality Functional Capacity Assessment Tool (VRFCAT) [32] is an interactive computerized measure of functional capacity. It presents the user with real life scenarios such as shopping, taking a bus, completing a recipe, etc, and assesses key instrumental activities of daily living (iADLS) in a realistic and interactive virtual environment. The VRFCAT has been accepted into the FDA's clinical outcome assessment (COA) as a measure of functional capacity for schizophrenia treatment trials. The VRFCAT has been shown to be a highly reliable and sensitive measure of functional capacity in patients with schizophrenia [33].

Secondary outcome measure, defined as improvement in cognitive functioning by ≥ 0.6 standard deviation (SD) and will be measured using tablet-based Brief Assessment of Cognition (BAC) cognitive assessment software [34]. We will assess and compare the changes in score from baseline (t0) to t1, and t2. Studies of computerized cognitive training (CCT) have found a change of 0.6–1 compared to the inactive treatment [35–37] with a maximum training effect of 0.15 SD [38]. As such, an effect size of 0.6 or more was considered as a threshold for the purpose of this study.

➢ The Brief Assessment of Cognition in Schizophrenia (BACS) [39]: is a tool to assess aspects of cognition found to be the most impaired and correlated with outcome in patients with schizophrenia. It consists of six domains: verbal memory, working memory, motor speed, attention and processing speed, verbal fluency and executive functioning.

We will be using alternative versions of both BACS and VRFCAT to reduce the practice effect. Having well-matched alternate forms has been shown to attenuate the practice effects with repeated cognitive assessments [40]. Also, all participants (despite the study arm) will complete the outcome measures at baseline, when most learning occur, which is another strategy to attenuate practice effect [41].

The VRFCAT and BACS software will be purchased from VeraSci. As per their license agreement, data collected from these measures (participant ID, visit number and measure results) will be stored on VeraSci servers and VeraSci can use combined data in an aggregate and anonymous manner. No identifying information from participants would be entered on the VeraSci servers or provided to VeraSci.

#### 3.4.1. Other measures

The Positive and Negative Syndrome Scale 6-item (PANSS-6) [42] will be used for monitoring psychotic exacerbation during the study. PANSS-6 will be administered at all study time points from t0-t3. Exacerbation is defined as any of the following criteria.

- Increase ≥3 from baseline on PANSS-6 while on study medication
- Change in clinical status, requiring a higher observation level (e.g change from routine observation to intermittent or constant observation as determined by the treating team)

Considering our patient population will have residual positive symptoms at baseline, and will therefore not be in remission, we considered "exacerbation" as a potential adverse outcome (as opposed to relapse). We could not find an operationalized definition of exacerbation in the literature and as such, we considered a combination of factors as mentioned above (a change in clinical status and rating scale score) as exacerbation criteria. This definition has been agreed upon by investigators of this study, which include clinical and clinician scientist experts in the field of schizophrenia.

➢ The PANSS-6 [42] is a 6-item version of the PANSS scale, and includes P1 = delusions, P2 = conceptual disorganization, P3 = hallucinations, N1 = blunted affect, N4 = social withdrawal, N6 = lack of spontaneity/flow of conversation. The PANSS-6 has been shown to adequately measure severity, remission, and antipsychotic efficacy related to core positive and negative symptoms in clinical trials [43] and its validity and sensitivity have been demonstrated in treatment resistant schizophrenia [44].

**Table 1**
study visits.

| Study Visit | Baseline (t0) | Week 1–3 | Week 4 (t1) | Week 5–7 | Week 8 (t2) | Week 12 (t3) |
|---|---|---|---|---|---|---|
| Assessment/Evaluation/Patient Info | X | | | | | |
| Obtain Consent | X | | | | | |
| Pregnancy Test | X | | | | | |
| Confirm Eligibility | X | | | | | |
| Medical History and Physical Exam | X | | | | | |
| Review Concomitant Meds | X | | | | | |
| Randomization | X | | | | | |
| Side Effect Form | | X | X | X | X | X |
| Medication Compliance/PRNs | | X | X | X | X | |
| Measurements (Weight, BP, Pulse) | X | X | X | X | X | X |
| VRFCAT | X | | X | | X | |
| BAC | X | | X | | X | |
| PANSS-6 | X | X | X | X | X | X |
| Assess for AEs | | X | X | X | X | X |

We chose to use the 6-item version of the PANSS to increase feasibility. The PANSS-6 takes much less time and is a good measure to identify exacerbation.

#### 3.4.2. Primary end point

Change from baseline in VRFCAT time to completion, number of errors, and forced progressions after 4 weeks of active treatment.

#### 3.4.3. Secondary end point

Change from baseline in neurocognitive function as measured by the neurocognitive composite score of the BAC after 4 weeks of active treatment.

#### 3.4.4. Training of qualified staff and interrater reliability

Anyone involved in study activities will be trained, will have GCP, TCPS2, SOP and Health Canada Division 5 training, and will be delegated on the delegation log. The BAC and VRFCAT are tablet-based measurements based on participants' performance and the scores will be calculated automatically. Research staff will be trained on providing instruction and guidance to participants.

For the PANSS-6, inter-rater reliability sessions will be held prior to study commencement until an IRC of minimum 0.80 is achieved. For the assessment of final interrater reliability, the raters will independently score all rating scales used in this study, and interrater reliability (IRC) will be calculated using Microsoft Excel.

### 3.5. Study timeline

This study has already received REB (REB#2021025) and Health Canada approval. This study has a Data and Safety Management Board (DSMB). Participants will enter into the study at different time points. We anticipate the approximate time for active recruitment of the 24 participants is estimated to be around 2–3 years.

## 4. Statistical analysis

a) Sample size calculation

The sample size was calculated using G Power 3.1.9.7. Using the Wilcoxon Signed Rank test for matched pairs, an a priori analysis indicated that a total sample size of N = 24 would provide sufficient power (at least 0.8) with alpha = 0.05 to identify a medium effect size (0.55) as significant. For the purpose of this study, we considered a minimum effect size of 0.55 of treatment intervention on cognitive symptoms. This effect size is estimated considering the findings of studies of cognitive treatment intervention (CCT) in schizophrenia, demonstrating an effect size of 0.6 to 1[35,36,37] as well as the overall efficacy of psychostimulants on cognition in the general adult population with ADHD (d = 0.67) [45]. As such, we anticipate at least a medium effect size of 0.55, considering the relatively high efficacy of psychostimulants on cognition, as well as the potential of improvement of cognition in this patient population with treatment intervention. Drop-outs will be replaced until the sample size is completed. Only participants who complete the 8 weeks of the trial will be included in the final analysis. We chose per protocol analysis, considering the primary outcome measure of this study focuses on efficacy. Participants who drop out of the study or discontinue the trial for any reason will be included in a descriptive report (i.e number of drop outs, reasons for drop out, side effects, etc).

Statistical criteria for early termination of study:

If after 18 months, the number of recruited participants is less than 10, the trial will be terminated for futility. The study will be terminated if 5 participants or more (~20 %) experience exacerbation.

a) Analysis plan

We will be using SPSS version 27.0 to conduct the Wilcoxon Signed Rank test for matched pairs, to compare the outcome measures among the two arms of the study.

In terms of sex and gender considerations, it is known that women have a later onset of schizophrenia than men [46]. Compared to men, women also respond better to antipsychotic medication and require lower doses of antipsychotics [46]. It is unclear what impact sex could have on response to adjunct methylphenidate in our sample. We hope to recruit a similar number of males and females. Our Outpatient Program serves a higher number of male patients (approximately 65 % are male based on internal program stats). However, the numbers are more even for our Recovery and inpatient units. For the fiscal year 2022–2023, 48 % of patients admitted to the Recovery Unit were male while 57 % admitted to the north/south inpatient units were male. We will collect information on both sex and gender. Given our small sample size (n = 24), a sex- and gender-based analysis will not be feasible. However, should this project lead to a larger study, a sex- and gender-based analysis will be carried out.

In developing this study protocol, we have been accessing statistical support through the Ottawa Method Centre at the Ottawa Hospitaland we will continue to rely on their guidance and assistance as we carry out this study.

## 5. Significance, impact and contribution

The proposed project intends to assess off-label use of adjunctive psychostimulants on functioning and cognitive symptoms in patients with schizophrenia. Established treatment guidelines do not provide any recommendations for pharmacological management of cognitive deficits in schizophrenia, yet such deficits are a major predictor of outcome in this patient population [47]. Americal Psychiatric Association (APA) guidelines recommends patients with schizophrenia to receive cognitive remediation, although the strength of evidence is not robust [48] and accessibility remains a challenge [8]. Adjunctive psychostimulants could be a potential treatment option to address cognitive deficits, in a subgroup of patients. Considering the risk for worsening or relapse of psychosis, use of adjunctive psychostimulants requires careful selection and monitoring of patients. In clinical practice, some patients are being prescribed off-label psychostimulants, yet the overall efficacy, tolerability and criteria for patient selection remains unclear. As such, this project will help to identify efficacy, and operationalize selection criteria and monitoring required for this patient population. Studies published to date on use of adjunctive psychostimulants either assessed response following acute administration (1–2 doses) or looked at participants with almost no residual positive symptoms (in remission). The novelty and significance of the current study is that it intends to investigate this intervention in a clinical setting, and assess applicability of it in a "real world setting" in a tertiary care hospital. To our knowledge, this would be the first RCT of subacute use of psychostimulants in patients with schizophrenia. Furthermore, this study is first of its kind to use virtual reality for assessment of functioning among patients with schizophrenia, treated with adjunctive psychostimulants. As such, this pilot project will add to the body of evidence related to treatment for schizophrenia as well as clinical management of this patient population.

## 6. Limitations

The limitations of this study include small sample size, the absence of placebo and the inherent limitations associated with the cross-over design. Due to the cross-over design, there is a hypothetical risk that the study medication (if taken first) might have carry over effects,

despite the short-half life. Carryover effects are generally less suspected in crossover trials on methylphenidate because of its short pharmacokinetic half-life. A meta-analysis of clinical trials of methylphenidate in ADHD found no signs of period effects or carryover effects in crossover trials [49]. Furthermore, if the hypothetical effect exits, it is expected to be fully diminished by the timing of the second outcome measures (week 8 testing), again due to short half-life.

## 7. Equity, diversity and inclusion in research practice and research

EDI in research design: EDI practices will be considered and integrated into our research study. We will seek to recruit and engage a diverse set of clients. All patients regardless of their age, gender, sex, sexual orientation, and ethnicity who are meeting eligibility criteria will have equal opportunity to participate in this study. We will aim to reduce barriers to participation through compensation to cover expenses such as bus fare/parking. We will collect information on diversity (gender, ethnicity etc) using a self-report questionnaire. Schizophrenia is an understudied/under-represented area in the literature. Another angel through which this study addresses EDI is by inclusion of an under-represented group of participants into research and with the goal of improving care for this group. EDI in research practice: For our team, we will promote diversity and foster an equitable, inclusive research environment. For example, the recruitment process for research staff will be equitable and we will use non-gendered, inclusive and unbiased language in any job posting. We will develop and maintain regular team communications/meetings and provide a safe space to discuss concerns. Furthermore, our research team and DSMB consist of women, various background/ethnicities and visible minorities.

## Ethics approval and consent to participate

This study has received ethical approval from the Royal Ottawa Hospital Research Ethics Board, and informed consent will be obtained from all participants.

## Consent for publication

Not applicable.

## Availability of data and materials

Not applicable.

## Funding

The investigators have received institutional funding through University Medical Research Fund (UMRF), for this project.

## Authors' contributions

NZ, AL, RJ, DA, PA designed the study and revised the methodology through the course of REB approval. NZ wrote the original protocol. CR and NZ made revisions of the protocol, obtained REB and Health Canada approval on behalf of the all investigators. DA, AL, CR assisted with the process of recruitment and enrollment of the participants (n = 5 so far).

## CRediT authorship contribution statement

**Naista Zhand:** Writing – original draft, Supervision, Methodology, Funding acquisition, Conceptualization. **David Attwood:** Writing – review & editing, Methodology, Conceptualization. **Alain Labelle:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Ridha Joober:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Carrie Robertson:** Writing – review & editing, Resources, Project administration, Funding acquisition. **Philip D. Harvey:** Writing – review & editing, Supervision, Methodology, Conceptualization.

## Declaration of competing interest

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

Dr. Harvey has received consulting fees or travel reimbursements from Alkermes, Bio Excel, Boehringer Ingelheim, Karuna Pharma, Merck Pharma, Minerva Pharma, and WCG Endpoint Solutions during the past year. He receives royalties from the Brief Assessment of Cognition in Schizophrenia (Owned by WCG, Inc. and contained in the MCCB). He is chief scientific officer of i-Function, Inc.

Other authors have no conflict of interest to declare.

## Data availability

No data was used for the research described in the article.

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