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

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I confirm that this study will be conducted in compliance with the protocol, the Tri-Council Policy Statement (TCPS2), ICH-GCP (Good Clinical Practice Guidelines) E6 (R2) and the Health Canada Division 5 Food and Drug Regulations.

Qualified Physician (responsible for medical decisions at the trial site)

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X _____ June 30, 2023
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Date:

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1. Introduction

Two of the major features of schizophrenia spectrum illness, negative and cognitive symptoms, have been associated with poor functional outcome and burden of illness[1]. Negative symptoms include alogia, flat affect, anhedonia, asociality and avolition[2]; cognitive symptoms include a broad array of deficits such as problems with working and verbal memory, attention, processing speed and executive function[3]. 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 and negative symptoms ranges from minimal to modest at best[4,5]. Numerous pharmacological augmentation strategies have been studied for the treatment of negative and/or cognitive symptoms with varying degrees of success. Nonetheless, to date there is no effective pharmacological treatment for either of these symptom clusters[6] 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[7], the effectiveness remain unclear to date in "real world" schizophrenia[8] and accessibility remains a clinical challenge[9]. In general, psychosocial interventions (including but not limited to cognitive remediation) remain poorly available to clinical populations with schizophrenia in the Western world: for instance, in 2010, only 15% of the 6007 participants with schizophrenia in the ESPASS cohort had access to any psychosocial intervention[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 negative[15] and/or cognitive symptoms of schizophrenia[6]. 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[16]. Other potential issues that arise with the use of psychostimulants in patients with psychosis include concerns regarding development of tolerance[17], rebound effect following discontinuation[6] and the potential for induction of super-sensitivity psychosis[18].

The preliminary results of earlier studies indicated improvement of negative symptoms with off-label use of adjunctive psychostimulants[19, 20, 21]; however, the use of psychostimulants has gradually faded in the schizophrenia literature considering the potential psychogenic role of these agents in this patient population[22]. 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[23]. 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[24]. 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[23,24].

A recent systematic review by Solmi et al (2018)[6] 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[6]. Nonetheless, the evidence remains inconclusive regarding adjunctive use of psychostimulants in schizophrenia.

Preliminary data:
In our retrospective chart review study[25] 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[23], 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 Schizophrenia 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:
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 will improve functional outcome in stable patients with schizophrenia in comparison to treatment as usual.

The secondary objective is:
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).

We hypothesized:
Adjunctive methylphenidate ER 36 mg will improve cognitive symptoms in stable patients with schizophrenia in comparison to treatment as usual.

3. Trial Design

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 (refer to section 3.3 for further details on selection of participants and eligibility). 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 (refer to section 3.4 for more details). The scales will be used for comparison analysis between active and control treatment arms. We are aiming to recruit a total of 24 participants (please refer to section 3.4 for primary and secondary endpoints).

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[26] (computer software).

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.

For the purpose of this study, we are aiming to recruit a total of 24 study participants and we will continue recruiting participants until we achieve this number.

Investigational Product Accountability

The Pharmacy at the Royal Ottawa Mental Health Centre will be responsible for ordering, storage and delivery of the product. As a licensed body, the Pharmacy follows all required regulations and hospital policies including the Medication Administration Policy, the Safe Medication Policy, the Controlled Substance Policy and the Pharmaceutical Waste Policy, and all pharmacy staff including the pharmacists and pharmacy technicians are regulated health care providers under the Ontario College of Pharmacists.

The product will be labelled and stored as per Health Canada guidelines. The product will be stored in the pharmacy in a secured location ie vault, in a temperature-controlled area (~22c). The temperature range for this medication is 15° - 30°C. The temperature will be checked and recorded daily as per clinical pharmacy protocol. Should a temperature excursion occur, Pharmacy will quarantine the investigational product, contact the manufacturer and release the inventory from quarantine once the integrity of the product is known.

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. The study medication will be stored in the Omnicell medication dispensing system, which has the built in capacity to regulate temperature, track and trace transactions. To ensure compliance with medication administration, dosing and disposal reports will be generated from Omnicell and EHR. If a dose is not given, the product would be returned to the Omnicell Return Bin, where it will be kept in quarantine until monitoring/auditing. Pharmacy staff would then empty this bin as part of standard practice and following relevant policies. Intact doses would be reused, while open packets would be disposed in the pharmaceutical waste bin.

For outpatients, the Pharmacy will drop off the study medication to the team each week and the medication will be dispensed to the participant by the research assistant during their weekly appointment. A dispensing log will be completed to track receipt and return of the study medication (see attached).

3.2. Selection and Withdrawal of Participants

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 the inpatient (north, south and Recovery) and outpatient units of the Schizophrenia Recovery Program. 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. We chose this specific population, considering 1) the advantage of monitoring patients in an inpatient setting by trained staff during the study period, and 2) the clinical stability of our outpatients.

Identification of Participants

Physicians (from the Schizophrenia Recovery Program) will be asked to identify eligible participants. Physicians and other Program staff will inform patients who meet eligibility criteria about the study and will ask if they are interested in speaking with the research assistant or a member of the research team. If the patient is interested in

learning more about the study, the patient will be asked to sign a Consent to Contact form (see Appendix B) and this form will be passed along to the research assistant. The research assistant will meet with the patient to explain the study, the requirements for participation and obtain informed consent.

Referral Requirement:

Participants who agree to be contacted for research and meet the referral eligibility criteria will be assessed for enrolment. Recruitment will be through referrals from treating psychiatrists who will assess that the following criteria are met (see Appendix A):

- 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

Informed Consent:

A written informed consent (Appendix C) 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.

Determination of capacity is based on the current capacity of participants to provide consent for treatment as ascertained by the treating psychiatrist, considering this trial is offering a treatment. Capacity to provide consent for treatment is assessed as part of the clinical standard. Based on clinical standard, capacity is considered the ability to understand and appreciate the benefits and risks associated with the proposed treatment. Participants who are incapable of making treatment decisions will be asked for assent and consent will be obtained from their SDM.

When participants are unable to give consent for the research study, consent will be obtained from their SDM. Participants will be asked for assent at the beginning of the study, and at the beginning of each study visit. If a participant does not give assent, the study visit will not continue, and assent will be sought at the next study visit.

During the course of the study, if the participant regains the ability to provide consent, the study team will go through the consent process with them. For participants who initially were able to consent to the study, but lose decisional capacity during the course of the study, the SDM will be asked to consent on their behalf. Assent will always be sought should this occur.

Of note, cognitive deficits are very common in schizophrenia (about 70% of patients with schizophrenia) and are among the core features of the illness[27]. Cognitive deficits in schizophrenia are not caused by global intellectual deficits and are not progressive[27]. Cognitive deficits in schizophrenia are independent of the state of the illness and do not fluctuate with severity of positive or negative symptoms[27]. As such, presence of cognitive deficits on testing, does not imply presence or absence of capacity for consent. Many patients with schizophrenia remain capable to provide consent for drug trials[28,29].

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. Have had treatment with ECT in the past 6 months
3. Have a documented history of traumatic brain injury
4. 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
5. 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
6. Have a diagnosis of substance induced psychosis
7. Have any of the following diagnoses: neurodevelopmental delay, intellectual disability, or neurocognitive disorder (dementia)
8. Have a diagnosis of another currently significant and unstable psychiatric condition (i.e. depressive episode, active substance use disorder, etc.)
9. Have a history of previous safety concerns directly driven by positive symptoms (e.g history of suicide attempt as directed by auditory hallucinations)
10. Have current active suicidality

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

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 (Appendix D.1). 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 (Appendix D.2). 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 (Appendix D.3) 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.

3.3. 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. It has a 3.5 hour half-life, reaches an initial maximum plasma concentration at about one hour followed by gradual ascending concentration over the next 5-9 hours. 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[30]. 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.

For inpatients, the study medication will be administered by a clinical registered nurse (RN) or a registered practical nurse (RPN), alongside their other medications.

Should day, overnight and/or weekend passes be granted, the study medication will be provided to patients as per standard care, in individual blister packs, along with their other regular medications. As per usual standard practice, inpatients returning from a pass will be asked to return the individual blister packs to their nurse. If a participant

is discharged from the inpatient unit during the study trial, they can continue in the study as an outpatient. If the participant is no longer a patient of the Royal and followed elsewhere, they will be withdrawn from the study.

Outpatients will receive the study medication at their weekly visit with the research assistant. The study medication will be provided to patients in individual blister packs. In order to monitor compliance, outpatients will be asked to complete a diary while on the study medication (see attached). They will also be asked to return the individual blister packs (used and unused) at their weekly visit.

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 hours for the medication. For the purpose of this study, we opted not to use a placebo due to feasibility issues. Our pharmacy does not have the capacity to produce identical placebo tablets and also, we were unable to access identical placebo through pharmaceutical companies. However, due to the nature of the study and after consultation with a statistician, we do not anticipate a significant negative impact on power due to the absence of placebo and blinding in this study, 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).
2) Our outcome measures are tablet-based computerized assessments. As such, raters (blinded or unblinded) could not impact the outcome.

Monitoring of participants during the study period: During the study period, participants will be monitored clinically by their treatment team as per standard clinical practice. Participants will also be asked to participate in a brief 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 the 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 (Appendix D.4). 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. They will be encouraged to ask any questions and whether they plan to continue with the study or not. If any psychiatric or medical concern is raised in a visit, then one of the onsite study investigators will be consulted. Depending on the nature and urgency of the concern, the patient will be scheduled to see a clinician, an onsite study investigator, or their primary clinician in the program. SDMs will not be required to attend weekly visits considering the ongoing documented consent. If any issues arise during the weekly visits that could potentially change the consent requirement, the SDM of the incapable participant will be notified.

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.

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 study 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[31]. 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[32].

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.

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)[33] 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[34].

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[35]. 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 to 1 compared to the inactive treatment[36,37,38] with a maximum training effect of 0.15 SD[39]. 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)[40]: 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[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.

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].

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.

Table of 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

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

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.

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.

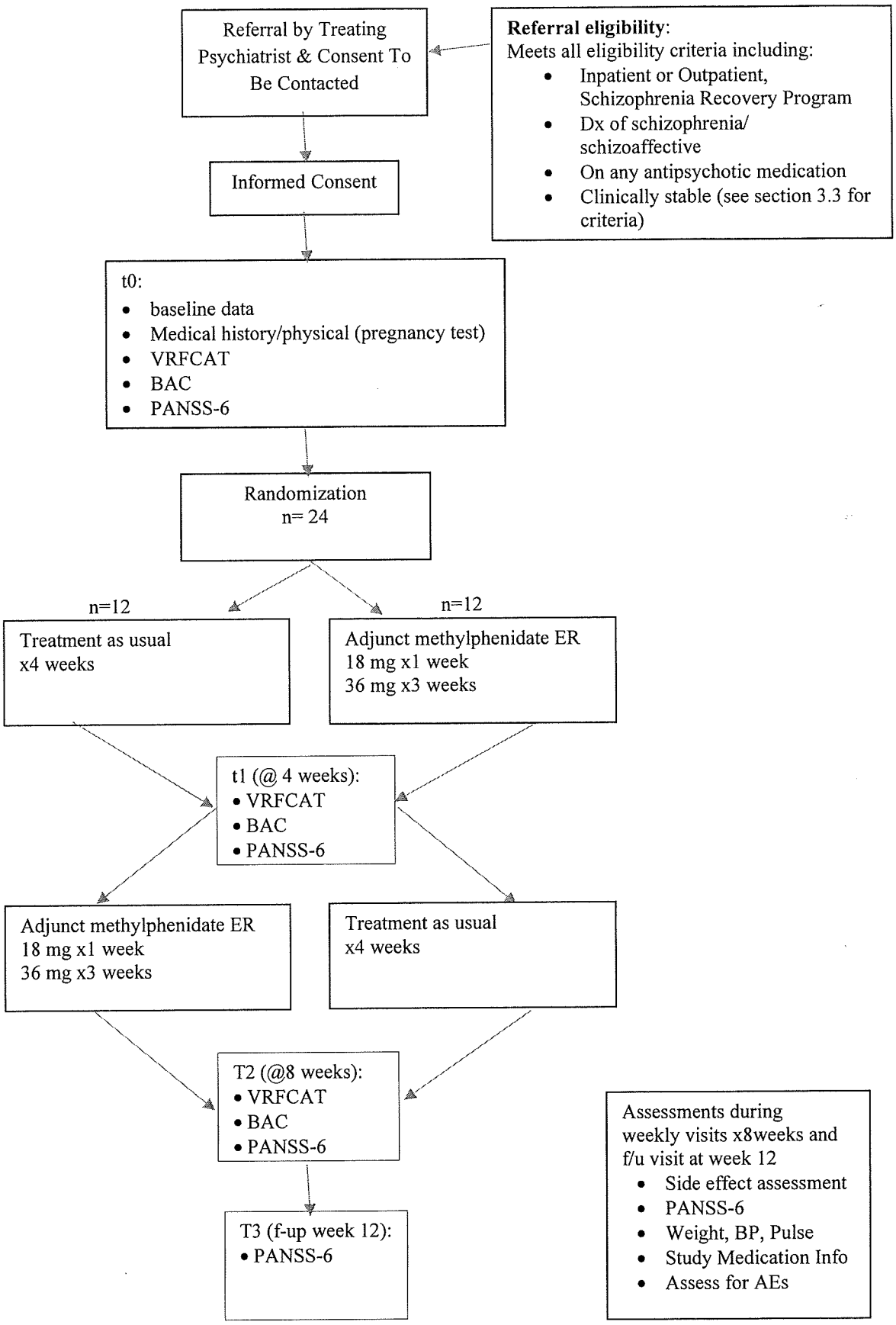
Management of Serious Adverse effects, Incidental Findings, Deviations:

- Based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 as defined by the US National Cancer Institute of the National Institutes of Health (NIH), an Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.

- Grade refers to the severity of the AE. As a general guideline, Grades 1-5 are described as the following: Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living. Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living. Grade 4 Life-threatening consequences; urgent intervention indicated. Grade 5 Death related to AE.
- Based on the CTCAE, Serious adverse events (SAEs) are defined as adverse events of Grade 4 or 5
- As defined by the US National Cancer Institute of the National Institutes of Health (NIH), an adverse drug reaction (ADR) is an unexpected medical problem that happens during treatment with a drug or other therapy. Adverse effects may be mild, moderate, or severe, and may be caused by something other than the drug or therapy being given. Also called adverse event.
- For the purpose of this study, we will assess AEs, SAEs and ADRs through: 1) Weekly visits with participants: (see section 3.3). 2) Medical reporting by the treating team: AEs and SAEs will be observed and reported by the clinical team. When an SAE occurs, causality will be assessed by the principal investigator. All severe AEs and SAEs will be assessed within 1 day by the principal investigator or the responsible site investigator. Any SAE (Grade 4, 5) or unexpected severe AE (Grade 3) that may reasonably be regarded as caused by, or probably caused by, the drug will be reported immediately to the REB (within 5 business day) and to Health Canada (within 7 days for Grade 4,5, and within 15 days for Grade 3). Severe expected AEs that are caused by or probably caused by the drug will be reported to the REB. All AEs and SAEs will be recorded on the relevant case report form (CRF) and/or the clinical record.
- The investigators of this study do not foresee any material incidental findings. In case of the discovery of unexpected incidental findings, the principal investigator and site investigator will determine whether the finding is material, and report the discovery to the REB, describing the process used to determine the materiality of the finding(s), and present a plan for disclosing such findings to the participants.
- The study team will keep a log of all deviations from the protocol (emergency or error). Deviations that impact safety and data integrity will be reported to the REB within 5 business days of the deviation occurring, or within 5 business days of the principal investigator becoming aware of the deviation.

3.5. Study timeline:

Upon receiving approval from the Research Ethics Board Committee, funding, and approval from Health Canada, recruitment of participants will begin. Participants will be entered into the study at different time points. We anticipate the approximate time for active recruitment of the 24 participants is estimated to be around 3 years.


Referral by Treating Psychiatrist & Consent To Be Contacted
Referral eligibility:
Meets all eligibility criteria including:
Inpatient or Outpatient, Schizophrenia Recovery Program
Dx of schizophrenia/ schizoaffective
On any antipsychotic medication
Clinically stable (see section 3.3 for criteria)
Informed Consent
t0:
baseline data
Medical history/physical (pregnancy test)
VRFCAT
BAC
PANSS-6
Randomization
n= 24
n=12
Treatment as usual
x4 weeks
n=12
Adjunct methylphenidate ER
18 mg x1 week
36 mg x3 weeks
t1 (@ 4 weeks):
VRFCAT
BAC
PANSS-6
Adjunct methylphenidate ER
18 mg x1 week
36 mg x3 weeks
Treatment as usual
x4 weeks
T2 (@8 weeks):
VRFCAT
BAC
PANSS-6
T3 (f-up week 12):
PANSS-6
Assessments during weekly visits x8weeks and f/u visit at week 12
Side effect assessment
PANSS-6
Weight, BP, Pulse
Study Medication Info
Assess for AEs

3.6. 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[36,37,38] 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 (please see our definition as described in the Other Measures section).

b) 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.

4.0 Direct Access to Source Data/Documents

The investigator(s)/institution(s) will permit trial-related monitoring, audits, REB review and regulatory inspection(s), providing direct access to source data/documents.

4. Trial Management:

Medical oversight will be provided as outlined in GCP and all study staff will be trained prior to commencing work on the trial. The specific tasks will be delegated on the delegation log.

4.3 The Trial Steering Committee and the Data and Safety Monitoring Committee:
The Trial Steering Committee will be comprised of members who collectively have the theoretical, statistical and clinical trial management experience to conduct the trial and analyze the results. Our Data and Safety Monitoring Committee will be informed systematically about adverse events. Our ethics committee at the Royal Ottawa Mental Health Centre and Health Canada will also be informed about any serious events.

Data Monitoring.
Please refer to Appendix E for details pertaining to the Data and Safety Monitoring Committee and the data monitoring plan.

5. Ethical Considerations

- *Research Ethic Board (REB) approval:* REB review and approval will be obtained prior to starting this project.

- *Health Canada approval*: will be obtained considering the off-label use of methylphenidate ER in patients with schizophrenia.

➢ *Informed consent:*

As described above, written informed consent will be obtained from eligible participants (and their SDMs if applicable). Participants will be informed about the voluntary nature of the study, and that they may refuse to participate or withdraw from the study at any time without impact on their treatment and care.

➢ *Participant compensation:*

Participants will receive $20.00 at every visit that they attend.

➢ *Confidentiality:*

Participants will be informed of the confidential nature of the study. All researchers involved in this project will sign the Privacy Acknowledgement Form, as required by the REB at the Royal Ottawa Mental Health Centre, and adhere to it. The following strategies will be used to protect the privacy and confidentiality of participants:

Data Handling:

The data produced from this study will be stored in locked filing cabinets in a secure office at the ROMHC. Electronic data will be stored in password-protected files on secured computers at the ROHCG. Only members of the research team will have access to the information.

Each participant will be assigned a unique study identification number to ensure participants' anonymity and confidentiality. This unique ID will be used on study questionnaires as well as for any other data entry. The master code list will be stored separately from study data. Consent forms will be housed separately from the study data; consent forms will be kept in separate locked filing cabinets. After study completion, the data will be kept for 15 years after the last publication of this study, as per Health Canada guidelines. This will ensure that researchers have access to data should they receive inquiries regarding the project. The data will then be destroyed.

The results of this study may be published or presented in public forums. However, no name or other identifying information will be used.

➢ *Conflict of interest:*

Currently, investigators of this project have no conflict of interest, or perceived conflict of interest in conducting this project; however, if there is a conflict of interest, or perceived conflict of interest, this will be clearly disclosed to the participants, and an amendment will be submitted to the REB.

5. Clinical significance

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 cognitive deficits in schizophrenia, neither pharmacological nor psychosocial[46], yet such deficits are a major predictor of outcome in this patient population[47]. 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.

Our team has the expertise required to carry out this project. NZ is a clinician researcher, with clinical expertise in the management of schizophrenia. AL has been involved in many treatment trials, in patients with schizophrenia. AL, AB and DA are senior clinical experts in the field of schizophrenia. PH is a world-known expert in schizophrenia and cognition research, and has been involved in numerous US and multi-centre clinical trials. CR is a Research Coordinator in the Schizophrenia Program who has been involved in several projects and clinical trials.

Limitations:

1) Due to small numbers, we may not be able to conduct a comparison of the effect of psychostimulants in clozapine versus non-clozapine patients. Clozapine has a unique effect and mechanism of action compared to other antipsychotics[48]; specifically, clozapine has markedly lower D2 receptor blockade compared to nearly all other antipsychotics[48], and is the gold-standard for treatment resistant schizophrenia due to its superior efficacy which has been attributed, at least in part, to its agonistic role at NMDA.[49,50]. Nonetheless, to increase feasibility we included patients on all antipsychotics, and it should be noted that our preliminary data did not show any significant differences between clozapine vs. non-clozapine patients[25].

Funding:

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