

Retrospective review of use of adjunctive psychostimulants in patients with schizophrenia

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BACKGROUND: Adjunctive psychostimulants have been proposed as a potential treatment option for the management of cognitive and/or negative symptoms of schizophrenia.

METHODS: The present study is a retrospective review of use of adjunctive psychostimulants among outpatients enrolled in our tertiary Schizophrenia Program between 2014 and 2019. We assessed response to treatment, adverse effects, and the impact of various clinical factors on treatment outcome.

RESULTS: Of the 77 (out of 1,300) participants prescribed psychostimulants during the study period, 42.22% had chart-based evidence of significant improvement, 27.77% had minimal improvement, and 25.55% reported no change. The majority (61.9%) demonstrated improvement in attention, concentration, and/or other cognitive symptoms. Approximately one-third of cases had evidence of emergence of psychosis. Of the factors assessed, comorbid attention-deficit/hyperactivity disorder was associated with an increased likelihood of response, and higher doses of stimulants were associated with likelihood of emergence of psychosis.

CONCLUSIONS: Adjunctive psychostimulants could be a potential treatment consideration to address cognitive deficits in selected patients with schizophrenia.

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INTRODUCTION

Negative and cognitive symptoms are core features of schizophrenia spectrum illness; both have been associated with poor functional outcome and burden of the illness.¹ Negative symptoms include alogia, flat affect, anhedonia, asociality, and avolition.² Cognitive symptoms contain 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-generation antipsychotics, is reasonably effective in adherent patients for positive symptoms; however, the efficacy of antipsychotics with respect to cognitive and negative symptoms ranges from neutral to modest at best.^{4,5} Numerous pharmacologic augmentation strategies have been studied for treatment of negative or cognitive symptoms, with varying degrees of success. Nonetheless, to date there is no effective treatment for either of these symptom clusters.⁶

In terms of pathophysiology, imbalance between cortical and subcortical dopamine systems has been implicated in schizophrenia. Dopaminergic hyperactivity in subcortical regions is implicated in pathophysiology of positive symptoms,⁷ and hypoactivity in the prefrontal cortex and mesocortical pathways has been attributed to negative and cognitive symptoms.⁸ Given the proposed role of dopaminergic hypoactivity, augmentation with psychostimulants has been postulated as a potential treatment option for negative⁹ 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 the use of stimulants in individuals with psychosis.¹⁰ Other potential issues that arise with the use of psychostimulants in patients with psychosis include concerns regarding development of tolerance,¹¹ rebound effect following discontinuation,⁶ and the potential for induction of supersensitivity psychosis.¹²

The preliminary results of earlier studies indicated improvement of negative symptoms with off-label use of adjunctive psychostimulants¹³⁻¹⁵; however, use of psychostimulants has gradually faded in the schizophrenia literature considering the psychogenic role of these agents in this patient population.¹⁶ A more recent open-label trial showed significant improvement of negative symptoms at Week 10 with adjunctive lisdexamfetamine in stable patients with schizophrenia.¹⁷ A randomized,

double-blind controlled trial that focused on safety and pharmacokinetics of lisdexamfetamine showed no significant change in negative symptoms but improvement in a measure of executive function and visual learning.¹⁸ A recent systematic review by Solmi et al⁶ did not find any evidence for efficacy of psychostimulants for negative symptoms. They reported potential improvement of cognitive symptoms with adjunct psychostimulants. However, the majority of studies in this review were psychostimulant challenge design (ie, acute administration of a single or few doses), and the review also included studies of non-dopaminergic stimulants (ie, 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 the adjunctive use of psychostimulants in schizophrenia. While many clinicians are hesitant to prescribe psychostimulants in patients with schizophrenia, the current evidence shows some preliminary potential in a selected group of patients. The present study aims to provide a descriptive review of the off-label use of adjunctive psychostimulants in a real-life setting, focusing on efficacy and safety, in a tertiary schizophrenia outpatient clinic.

Furthermore, we intended to 1) compare the safety and efficacy of short- vs long-acting stimulants, and 2) assess the efficacy of adjunctive psychostimulants when added to clozapine in comparison to nonclozapine antipsychotics. We were interested in this comparison considering the unique effects and mechanism of action of clozapine compared with other antipsychotics because clozapine has markedly lower D2 receptor blockade compared with nearly all other antipsychotics¹⁹ and is the gold-standard for treatment-resistant schizophrenia due to its superior efficacy. *N*-methyl-D-aspartate (NMDA) receptor hypofunction has been proposed in pathophysiology of schizophrenia²⁰ and the agonistic role of clozapine at NMDA has been postulated in its superior efficacy.^{21,22}

METHODS

This is a retrospective review of electronic medical records on the use of adjunctive psychostimulants among outpatients enrolled in our tertiary Schizophrenia Program at the Royal Ottawa Mental Health Centre, between May 31,

2014 and June 1, 2019. This study was approved by the Research Ethics Board of the hospital. We included all patients, regardless of age or comorbidities. Patients who did not have a diagnosis of schizophrenia spectrum illness or schizoaffective disorder were excluded.

Study design and participants

All psychiatrists in the Schizophrenia Program were approached for the initial screening of potential participants. The psychiatrists identified 728 participants who were not prescribed stimulants in the past 5 years. For the remaining 592 participants, the physician's progress notes between 2014 and 2019 were reviewed by researchers (AH and MS). Twenty patients were excluded because they had a diagnosis other than schizophrenia spectrum illness. The initial review identified 77 patients who were prescribed psychostimulants during the study period. Electronic medical records of these 77 patients were reviewed by 2 researchers (NZ and RO) independently. For patients who were prescribed dopaminergic psychostimulants during the study period, the following information was collected using an investigator-generated questionnaire: demographics, diagnoses, medications, substance use, presence of positive symptoms, and information pertaining to treatment with psychostimulants, including efficacy and adverse effects. A retrospective modified Clinical Global Impression-Improvement (CGI-I)²³ scale was filled out by the 2 clinical raters (NZ and RO) independently and consensus was achieved for cases with different ratings.

Psychostimulants

Dopaminergic psychostimulants prescribed in this study included methylphenidate (Ritalin), methylphenidate extended-release (Concerta), mixed amphetamine salt extended-release (Adderall XR) and lisdexamfetamine (Vyvanse). Psychostimulants were classified as short- or long-acting methylphenidate-based stimulants (methylphenidate and methylphenidate extended-release) and short- or long-acting amphetamine-based (mixed amphetamine salt extended-release and lisdexamfetamine, respectively). The mixed amphetamine salt extended-release is a combination of immediate- and delayed-release pellets and has a total half-life of 12 hours. The first half of the dose is released upon ingestion and results in steep dopaminergic stimulation; the delayed-release pellets provide the long coverage of the mixed amphetamine salt extended-release.²⁴ Thus, we classified mixed amphetamine salt extended-release as a

short-acting agent for comparison considering its immediate release properties, which is different from the slow and steady release of lisdexamfetamine.

The dose of psychostimulants was classified as:

- low: starting dose and below
- mid: dose range between starting dose and the highest recommended dose
- high: the maximum recommended dose
- above maximum.

Main outcome measures

For the purpose of this study, we were interested in identifying the potential impact on symptomatology as well as the potential emergence of psychosis as a result of adjunct psychostimulants. Two main outcome measures were used.

Improvement and modified CGI-I. Data were collected on 1) the target symptom domain for which the stimulants were prescribed as noted in the medical record, and 2) the symptom domain that was noted to be changed as a result of treatment with the adjunctive stimulant. We used a modified version of the CGI-I for the latter. Considering the retrospective nature of this review, distinguishing “much” improved/worse and “very much” improved/worse could be subjective in some cases, and as such we decided to combine those items on the CGI-I and instead of rating from 1 to 7 we used the following modified version:

- 1 = much (and very much) improved
- 2 = minimally improved
- 3 = no change
- 4 = minimally worse
- 5 = much (and very much) worse

Symptom domains were captured based on the clinical documentations of the treating psychiatrists and included: 1) lack of motivation, 2) low energy/sedation, 3) attention/concentration and other cognitive symptom descriptors, 4) attention-deficit/hyperactivity disorder (ADHD) symptoms/comorbid diagnosis, 5) depressed mood, and 6) other.

Emergence/worsening of psychosis. To avoid confusion, we recorded emergence or worsening of psychosis separate from the symptom domains scored by the CGI-I in our study. Patients may experience improvement in their motivation and worsening of their psychosis at the same time. Emergence or worsening of psychosis was defined as emergence of new or worsening of pre-existing positive symptoms concurrently with stimulant

TABLE 1
Clinical characteristics of the participants

Clinical characteristic	Category	%
Comorbidities	None	49.35%
	Substance use disorder	24.66%
	Anxiety disorder	20.77%
	Neurodevelopmental	6.49%
	Trauma	5.19%
	Others	6.49%
Description of substance use	No substances	50.64%
	Unknown	7.79%
	In remission	16.88%
	Polysubstance	12.98%
	Cannabis	9.09%
	Alcohol	1.29%
	Cocaine	1.29%
Presence of positive symptoms prior to initiation of psychostimulants	Yes	40%
	No	54.44%
	Unknown	5.55%
Number of antipsychotic medications (mean: 1.56)	None	3.33%
	1	51.11%
	2	33.33%
	3	11.11%
	4	1.11%
Antipsychotic medications ^a	Aripiprazole	53.33%
	Clozapine	36.66%
	Olanzapine	20%
	Quetiapine (>300 mg)	12.22%
	Paliperidone	11.11%
	Risperidone	6.66%
	Lurasidone	5.55%
	Brexipiprazole	4.44%
	Methotrimeprazine	2.22%
	Zuclopenthixol	1.11%
	Ziprasidone	1.11%
	Chart-based description of the reason for prescription of stimulants (by psychiatrist)	Unknown
Lack of motivation		15.55%
Low energy/sedation		34.44%
Attention/concentration		64.44%
ADHD		6.66%
Low mood		6.66%
Decrease substance use		2.22%

^aTotal percentage is >100% because some patients received ≥ 2 antipsychotics.

ADHD: attention-deficit/hyperactivity disorder.

co-prescription, with a severity that required treatment intervention, including adjustment of antipsychotic medication and/or psychiatric admission.

Statistical analysis

We used Microsoft Excel (2012) to run a basic descriptive statistical analysis. For comparison analysis, we conducted Chi-square tests using IBM SPSS Statistics version 26.

RESULTS

Characteristics of the participants

During the study period, 5.92% of patients (77/1,300) were prescribed adjunctive psychostimulants. The majority of patients (84.4%) had 1 trial, 14% of patients had 2 trials, and 1.3% of patients had 3 trials of psychostimulants. A total of 90 separate trials were included in the analysis. Of the total of 77 participants, 54 (70.12%) were male. The mean (standard deviation [SD]) age of participants who were prescribed stimulants was 35.53 (12.72) years; 62.33% had a diagnosis of schizophrenia, and the remaining 37.66% had schizoaffective disorder. Eleven patients (14.28%) had a comorbid diagnosis of ADHD. The mean (SD) duration of follow-up was 4.22 (1.25) years, ranging from 4 months to 5 years. Overall, 36.66% of patients were receiving clozapine, with a mean (SD) dose of 289.66 mg (137.5 mg) and a dose range of 50 to 550 mg; 23.37% of participants were receiving a long-acting injectable (LAI) antipsychotic medication. **TABLE 1** summarizes the participants' clinical characteristics.

Psychostimulants used

Stimulants prescribed during the study period included methylphenidate extended-release (60%), methylphenidate (5.55%), lisdexamfetamine (10%), and mixed amphetamine salt extended-release (24.44%). The majority of patients (63.32%) were prescribed either low-range (24.44%) or mid-range (38.88%) doses; however, a good proportion were also prescribed high-range (22.22%) and above maximum (14.4%) doses. The mean (SD) duration of stimulant trial was 17.54 (18.89) months, ranging from 0.05 to 60 months.

Response and outcome

As for the clinical response, 38 out of 90 trials (42.22%) had chart-based evidence of significant improvement, slightly less than one-third (27.77%) had minimal

improvement, and 25.55% reported no change. The outcome was unknown for 4.44%.

Of those patients who demonstrated improvement, the majority (61.90%) reflected improvement in attention, concentration, and/or other cognitive symptoms. In addition, 39.68% had improvement in symptoms of low energy and sedation, 9.52% showed improvement in ADHD symptoms, and 9.52% had improvement in amotivation. Also, 7.93% had improvement in symptoms of low mood, and reduction of substance use was reported in one patient (1.58%). The total percentage exceeds 100% because some patients had improvement in >1 domain.

Approximately one-third ($n = 27$) of patients had evidence of the emergence of psychosis related to the psychostimulant trial. Of the patients experiencing emergence of psychosis, 7/27 (25.92%) required psychiatric admission. Of those requiring admission, the majority (85.71%) had received psychostimulant doses of maximum or above. Due to an overall small number ($n = 7$), we were unable to perform a comparison analysis of associated factors with the increased rate of admission. Considering the clinical and retrospective nature of this study, we were unable to make inference about supersensitivity psychosis as a potential underlying mechanism for worsening/emergence of psychosis.

Approximately 54.44% of patients discontinued adjunct psychostimulants during the follow-up period. Reasons for discontinuation included psychotic symptoms (44.89%), lack of efficacy (22.44%), psychiatric adverse effects other than psychosis (eg, worsening of anxiety [20.40%]), medical adverse effects (eg, increased blood pressure [10.20%]), and other reasons (eg, patients stopped all medications [14.28%]).

Of the 44.44% who continued the psychostimulant trial, the mean (SD) duration of the trial was 28.17 (21.21) months, and the mode was 23 months.

Our retrospective review found no chart-based evidence of the development of tolerance to psychostimulants and no evidence of rebound effect following the discontinuation of psychostimulants.

Clinical factors and impact on outcome measures

We assessed the impact of the following factors on response and emergence of psychosis: diagnosis (schizophrenia vs schizoaffective), comorbid ADHD, concurrent substance use, presence of positive symptoms prior to stimulant trial, specific psychostimulant and dose,

short- vs long-acting psychostimulant, treatment with clozapine, antipsychotic change during stimulant trial, and treatment with LAIs.

Of the factors assessed, presence of comorbid ADHD was associated with increased likelihood of improvement ($P < .05$) and high-dose psychostimulants were associated with higher risk of emergence of psychosis ($P < .05$). **TABLE 2** summarizes these findings.

DISCUSSION

The current study is notable for 1) providing a comprehensive and detailed review of off-label use of adjunctive psychostimulants in patients with schizophrenia in a real-life setting, and 2) assessing the clinical status of these participants up to 5 years in follow-up; 80.51% of patients had a follow-up period of 4 years or more.

During the study period, approximately 6% of patients in our Schizophrenia Program were prescribed psychostimulants. While currently there are no treatment guidelines for prescribing adjunctive psychostimulants in patients with schizophrenia, it appears that the treating psychiatrists selected this subgroup of participants carefully. This is evidenced by the demographics of our participants, including a lower rate of psychiatric comorbidities and substance use, as well as a lower average clozapine dose. Approximately one-half of the participants who were prescribed psychostimulants had no other psychiatric comorbidities, and only approximately 24% had a concomitant substance use disorder. These observed numbers are much lower than the rate of comorbidities and substance use (41.7%) in patients with schizophrenia.²⁵ The prevalence of psychiatric comorbidities in patients with schizophrenia is estimated at 29% for posttraumatic stress disorder (PTSD), 23% for obsessive-compulsive disorder, and 50% for comorbid depression²⁶; however, in this cohort of patients we observed much lower rates of PTSD and depression, and no patients with comorbid obsessive-compulsive disorder were prescribed psychostimulants.

Nonetheless, it is important to highlight that the rate of psychostimulant use was relatively low in this study, and it remains unclear as to whether greater use of psychostimulants would lead to more adverse effects or a better outcome. Another point worth mentioning is that our Schizophrenia Program focuses on tertiary-level schizophrenia care; therefore, patients enrolled in

TABLE 2
Impact of clinical factors on outcome measures

Clinical factor	Response	Psychosis
ADHD	Chi-square (2, <i>N</i> = 73) = 7.590, <i>P</i> = .022	Chi-square (1, <i>N</i> = 77) = 0.837, <i>P</i> = .360
Substance use	Chi-square (2, <i>N</i> = 67) = 1.005, <i>P</i> = .605	Chi-square (1, <i>N</i> = 71) = 0.004, <i>P</i> = .948
Type of stimulant (methylphenidate [Ritalin], methylphenidate extended-release [Concerta], mixed amphetamine salt extended-release [Adderall XR] and lisdexamfetamine [Vyvanse])	Chi-square (6, <i>N</i> = 86) = 7.174, <i>P</i> = .305	Chi-square (3, <i>N</i> = 90) = 0.861, <i>P</i> = .835
Long- vs short-acting stimulant	Chi-square (2, <i>N</i> = 86) = 1.677, <i>P</i> = .432	Chi-square (1, <i>N</i> = 90) = 0.305, <i>P</i> = .581
Dose of stimulant	Chi-square (6, <i>N</i> = 86) = 3.175, <i>P</i> = .787	Chi-square (3, <i>N</i> = 90) = 8.372, <i>P</i> = .039
Diagnosis (schizophrenia vs schizoaffective)	Chi-square (2, <i>N</i> = 73) = 1.496, <i>P</i> = .473	Chi-square (1, <i>N</i> = 77) = 2.942, <i>P</i> = .086
Presence of positive symptoms	Chi-square (2, <i>N</i> = 83) = 4.917, <i>P</i> = .086	Chi-square (1, <i>N</i> = 85) = 0.897, <i>P</i> = .344
Treatment with clozapine	Chi-square (2, <i>N</i> = 86) = 0.619, <i>P</i> = .734	Chi-square (1, <i>N</i> = 90) = 1.916, <i>P</i> = .166
Antipsychotic change during stimulant trial	Chi-square (2, <i>N</i> = 86) = 1.598, <i>P</i> = .450	Chi-square (1, <i>N</i> = 90) = 2.156, <i>P</i> = .142
Treatment with LAI antipsychotic	Chi-square (2, <i>N</i> = 86) = 5.525, <i>P</i> = .0613	Chi-square (1, <i>N</i> = 90) = 0.156, <i>P</i> = .693

ADHD: attention-deficit/hyperactivity disorder; LAI: long-acting injectable.

our Schizophrenia Program are usually more complex, chronic, and have a high rate of treatment resistance. As such, this result may not necessarily be generalizable to all patients with schizophrenia.

We observed chart-based evidence of significant improvement in a good proportion (42.22%) of our participants, with the majority showing improvement in attention, concentration, or other reported cognitive symptoms. This result is in keeping with the findings from the review by Solmi et al⁶ and highlights the potential therapeutic role of psychostimulants in addressing cognitive deficits in selected patients with schizophrenia.

Approximately one-third of our participants experienced the emergence of psychotic symptoms as a result of treatment with stimulants. Of the factors assessed, overly high doses of psychostimulants were associated with increased likelihood of emergence of psychosis. This result signifies the importance of careful selection of patients, close monitoring during the stimulant trial, and the use of low to moderate doses of psychostimulants in this patient population.

We compared the outcomes of patients receiving clozapine vs patients who did not receive clozapine for several reasons. As mentioned earlier, clozapine's mechanism of action differs from that of other antipsychotics; furthermore, since clozapine is prescribed for

patients with treatment-resistant schizophrenia, in general, patients receiving clozapine vs patients who did not receive clozapine represent different phenotypes, and therefore could exhibit different responses to treatment interventions. Nonetheless, we did not find any difference in outcomes between the 2 groups. One potential explanation is that the efficacy and safety of adjunct psychostimulants is not directly related to a particular phenotype (ie, treatment-resistant vs treatment-responsive depression) and/or the mechanism of action of clozapine. Rather, a combination of factors may impact the overall outcome. However, because a number of potential confounding factors were not controlled for in this study, such observed negative association needs to be interpreted cautiously. The potential confounding factors include a lack of information about adherence and positive and cognitive symptom severity prior to the stimulant trial. We also did not find any significant difference in outcomes comparing short- vs long-acting stimulants. Future studies examining such a comparison in a controlled setting are recommended.

Limitations

Methodological limitations of the current study include the inherent limitations of retrospective chart review and the absence of a control group. The absence of use

of standardized measures renders our findings preliminary and signifies the need for future randomized controlled trials.

CONCLUSIONS

Adjunctive psychostimulants could be a potential treatment consideration to address cognitive deficits in selected patients with schizophrenia. Our results are helpful in predicting the rate and degree of clinical response, potential adverse effects, and associated factors. Further prospective studies are recommended in this patient population, using standardized cognitive testing and a control group for comparison of outcomes. Furthermore, we suggest consideration of the impact on quality of life and functional outcome, since neurocognition is a major predictor of outcome in this patient population.²⁷

We also suggest future studies look into identifying criteria of the subgroup of patients who may have less risk of emergence of psychosis and are therefore more suitable for a psychostimulant trial. Use of LAIs as a base antipsychotic treatment is highly recommended because in general, the superiority of LAIs in reducing rate of relapse, readmission, and increased medication adherence in this patient population is well established,^{28,29} and therefore LAIs might mitigate the risk of adverse outcome

(ie, worsening of psychosis) associated with adjunctive psychostimulants. Another factor to consider is the optimal use of slow-release, long-acting psychostimulants. Although our results did not find any difference in outcome between long- and short-acting psychostimulants, the long-acting psychostimulants have features that make them a more relevant option for use in schizophrenia. Short-acting psychostimulants are usually associated with a steeper peak of increased dopamine, requiring twice-daily dosing with a resultant higher second peak, and a fluctuating peak and trough of dopamine.^{30,31} In particular, this becomes relevant to patients with schizophrenia who are more sensitive to dopaminergic stimulation. ■

DISCLOSURES: Dr. Harvey has received research support from Takeda and the Stanley Medical Research Foundation. He has received consulting fees or travel reimbursements from Acadia Pharma, Alkermes, Bio Excel, Boehringer Ingelheim, Minerva Pharma, Otsuka Pharma, Regeneron Pharma, Roche Pharma, and Sunovion Pharma during the past year, and receives royalties from the Brief Assessment of Cognition in Schizophrenia. He is Chief Scientific Officer of i-Function, Inc. None of these companies provided any information to the authors that is not in the public domain. The other authors report no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

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