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Optimal Use Report

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Optimal Use Recommendations for Atypical Antipsychotics: Combination and High-Dose Treatment Strategies in Adolescents and Adults with Schizophrenia

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment in respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report.

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1 INTRODUCTION

Optimizing drug-related health outcomes and cost-effective use of drugs by identifying and promoting optimal drug prescribing and use is a goal of the Canadian Agency for Drugs and Technologies in Health (CADTH). Where possible, CADTH builds on existing applicable Canadian and international initiatives and research. CADTH goals are achieved through three main approaches:

- Identifying evidence-based optimal use in prescribing and use of specific drugs
- Identifying gaps between clinical practice, then proposing evidence-based interventions to address these gaps
- Supporting the implementation of these interventions.

Direction and advice are provided to CADTH through various channels, including the following:

- The Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) Advisory Committee (CAC) and the Advisory Committee on Pharmaceuticals (ACP) include representatives from the federal, provincial, and territorial health ministries and related health organizations
- The COMPUS Expert Review Committee (CERC; members are listed in Appendix 1)
- Stakeholder feedback.

Note: in 2010, the CAC and ACP were replaced by the Drug Policy Advisory Committee (DPAC) and DPAC Optimal Use Working Group (OUWG) and Formulary Working Group (FWG).

1.1 COMPUS Expert Review Committee

CERC consists of eight Core Members appointed to serve for all topics under consideration during their term of office and three or more Specialist Experts appointed to provide their expertise in recommending optimal use for one or more specific topics. For topics in the area of mental health, four specialists were appointed as Specialist Experts. Two of the Core Members are Public Members who bring a lay perspective to the committee. The remaining six Core Members hold qualifications as physicians, pharmacists, or health economists or have other relevant qualifications, with expertise in one or more areas such as, but not limited to, family practice, internal medicine, institutional or community clinical pharmacy, pharmacoeconomics, clinical epidemiology, drug utilization expertise, methodology, effecting behaviour change (through health professional and/or patient and/or policy interventions), and critical appraisal. The Core Members including Public Members are appointed by the CADTH Board of Directors.

The mandate of CERC is advisory in nature and consists of providing recommendations and advice to CADTH on assigned topics that relate to the identification, evaluation, and promotion of optimal practices in the prescribing and use of drugs across Canada. The overall perspective used by CERC members in producing recommendations is that of public health care policy-makers in pursuit of optimizing the health of Canadians within available health care system resources.

2 ISSUE

CAC and ACP have identified atypical antipsychotics (AAP) for schizophrenia: high-dose and combination therapy as being a priority topic for optimal practice initiatives based on the following criteria:

- Large deviations from optimal utilization (overuse or underuse)
- Size of patient populations
- Impact on health outcomes and cost-effectiveness
- Benefit to multiple jurisdictions
- Measurable outcomes
- Potential to effect change in prescribing and use.

2.1 Schizophrenia

Schizophrenia is a mental illness that requires lifelong treatment[1] and is associated with symptoms that include hallucinations, delusions, cognitive impairment, disorganized thoughts, social withdrawal, and amotivation.[2] Its worldwide prevalence is 0.5% to 1.5%,[3] and in Canada it affects about 1% of the population,[2] or about 234,305 (95% CI: 136,201 to 333,402) people (2004 data).[4] Schizophrenia is a chronic or recurrent illness and patients are at an increased risk for numerous other medical illnesses, and risks for suicide and substance abuse, homelessness, and unemployment.[5]

The total financial burden of schizophrenia in Canada was estimated to be C$6.85 billion in 2004.[6] The annual direct health care and non-health costs were estimated at C$2.02 billion (2004 dollars); acute (23%) and non-acute (38%) hospital care accounted for the majority of these costs.[6] Diagnostic criteria for schizophrenia are currently based on the latest revisions of either the World Health Organization International Statistical Classification of Diseases and Related Health Problems (ICD-10) or the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV).[3]

2.1.1 Management of schizophrenia

Antipsychotic medications form the cornerstone of treatment for schizophrenia,[2] as they target the characteristic symptoms of the disease.[3] These symptoms can be positive or negative in nature.[3] Positive symptoms reflect a distortion or abundance of normal functions and negative symptoms reflect a loss or restriction of normal function.[7] Positive symptoms include hallucinations and delusions, while negative symptoms include affective flattening, loss of interest, and alogia (lack of speech).[7] The underlying principles in place for the administration of pharmacotherapy include the individualization of medication (the tailoring of treatment for each patient, which includes consideration of patient preferences), simple medication regimens, appropriate dosing, attention to side effect profiles, regular evaluation of responses in general (including adverse events),[5] and short- and long-term clinical efficacy, safety, and tolerability.[1]

Although there have been important developments in this area over the last 40 years, about one-third of persons with schizophrenia have a poor response to antipsychotic medications.[8] Surveys of prescribing practices in the United Kingdom (UK) showed that the use of doses higher than those usually recommended is common, when antipsychotic agents are used either alone or in combination with another antipsychotic medication.[8] Also, although combination therapy with two antipsychotic agents is not recommended in current clinical

management guidelines,[5] with the exception of combination therapy with clozapine,[8] it appears this practice is not uncommon.[8,9] Two longitudinal studies from the United States (US) reported that 9.5% to 22.0% of patients with schizophrenia received two antipsychotic agents concurrently.[10,11] The proportion of patients treated with more than one AAP (antipsychotic polypharmacy) increased from 3.3% in 1999 to 13.7% in 2004.[10] Data from British Columbia indicate that the rate of antipsychotic polypharmacy increased between 1996, when an estimated 28% of patients discharged from hospital were on polypharmacy, compared with 45% in 2000. For patients using clozapine, the rate of polypharmacy increased from 22% in 1996 to 53% in 2000.[12] Reasons identified for this increasing prevalence include the use of as-required (PRN) medication, the gradual switch (bridging) from one antipsychotic to another one, as well as the combination of two antipsychotic medications to achieve greater therapeutic response when there has been an unsatisfactory response to a single antipsychotic.[8] Overall prevalence rates of antipsychotic polypharmacy range from 4% to 58%,[9] and rates up to 69%[12] have been reported, depending on treatment setting and patient population.

2.1.2 Technology description — atypical antipsychotics

Most existing antipsychotic therapies fall into one of two classes. The typical antipsychotics (TAP; also known as conventional antipsychotics or neuroleptics) are of the first-generation antipsychotic class. The atypical antipsychotics (AAP) are of the second-generation antipsychotic class.

Seven AAPs are currently available in Canada: aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone (Table 1). Two other AAPs, asenapine and iloperidone, were recently approved in the US, while sulpiride and amisulpride are available in the European Union.

Table 1: List of Atypical Antipsychotics Available in Canada and US

Generic Name	Trade Name	Dose Range	Definition of High Dose†	Manufacturer
Aripiprazole	Abilify	10–15 mg/d	> 30 mg/d	Bristol-Myers Squibb
Asenapine*	Saphris	10 mg/d (5 mg bid)	> 10 mg/d	Schering-Plough
Clozapine	Clozaril	300–600 mg/d	> 600 mg/d¶	Novartis
Olanzapine	Zyprexa, Zyprexa Zydis	5–10 mg/d	> 20 mg/d	Eli Lilly
Olanzapine*‡	Zyprexa Relprevv	150–300 mg/2 wk	> 300 mg/2 wk (405 mg/4 wk)	Eli Lilly
Iloperidone*	Fanapt	12–24 mg/d (administered 6–12 mg, bid)	> 24 mg/d	Titan Pharmaceuticals
Paliperidone	Invega	6–12 mg/d	> 12 mg/d	Janssen-Ortho
Paliperidone injection‡	Invega Sustenna	39–234 mg/mo	> 234 mg/ mo	Janssen-Ortho
Quetiapine	Seroquel	300–800 mg/d	> 800 mg/d	AstraZeneca
Quetiapine	Seroquel XR	400–800 mg/d	> 800 mg/d	AstraZeneca

Table 1: List of Atypical Antipsychotics Available in Canada and US				
Generic Name	**Trade Name**	**Dose Range**	**Definition of High Dose†**	**Manufacturer**
Risperidone	Risperdal Risperdal M-Tab	4–6 mg/d	> 6 mg/d§	Janssen-Ortho
Risperidone injection‡	Risperdal Consta	25–50 mg/2 wk	> 50 mg/2 wk	Janssen-Ortho
Ziprasidone	Zeldox	120–160 mg/d	> 160 mg/d	Pfizer

d = day; mo = month; wk = week.
* Approved by the US Food and Drug Administration (FDA) but not available in Canada.
† Based on expert clinical opinion, the definition of high dose for each agent was the maximal dose recommended in the Canadian product monograph, unless otherwise indicated.
‡ Long-acting injectable agent.
§ Maximum according to product monograph is 16 mg per day.
¶ Maximum according to product monograph is 900 mg per day.

3 OBJECTIVE

The objectives of this report are to provide recommendations for the optimal prescribing and use of AAP combination and high-dose treatment strategies in adolescents and adults with schizophrenia or schizoaffective disorder inadequately controlled on standard-dose antipsychotic monotherapy.

4 PROJECT OVERVIEW

Once a topic is selected, CADTH undertakes activities related to key areas in the procedure. The OUWG, formed after topic identification, will provide advice and guidance throughout the process, through to supporting intervention and evaluation tools. CERC provides expert advice and recommendations on the topic area regarding the identification, evaluation, and promotion of optimal prescribing and use of drugs. A broad range of stakeholders are invited to provide feedback at key stages in the CADTH process.

This report represents the Optimal Use Recommendations step in the process.

5 RESULTS

5.1 Optimal Use Recommendations

Through careful evaluation of the evidence (Section 6) and significant deliberation of the issues (Section 7), CERC produced four recommendations on the use of AAP combination and high-dose treatment strategies in adolescents and adults with schizophrenia inadequately controlled on standard-dose antipsychotic monotherapy. These have been grouped into two summary recommendations, as shown in Table 2 below.

Table 2: COMPUS Expert Review Committee Recommendation for Combination and High-Dose Treatment Strategies with Atypical Antipsychotics
• CERC recommends that clozapine-based antipsychotic combination therapy should not be used for patients with schizophrenia who inadequately respond to standard-dose clozapine monotherapy.* * The available data for combination therapy with clozapine were primarily for oral risperidone, with some evidence available for aripiprazole and sulpiride. There was no evidence available for other atypical antipsychotic agents.
• CERC recommends that non–clozapine-based atypical antipsychotic combination therapy should not be used for patients with schizophrenia who inadequately respond to a standard-dose atypical antipsychotic agent.* * Evidence was available only for the combination of risperidone or quetiapine with aripiprazole. There was no evidence for other combinations involving atypical antipsychotic agents.
• CERC recommends that standard-dose clozapine should be used instead of high doses of other atypical antipsychotic agents for patients with schizophrenia who inadequately respond to a standard-dose atypical antipsychotic agent.* * Evidence was available only for use of high-dose risperidone and high-dose olanzapine. There were no studies comparing other atypical antipsychotic agents used at high doses with standard-dose clozapine. Of note, the threshold for defining high-dose olanzapine in the CADTH systematic review was higher than Health Canada–approved doses.
• CERC recommends that high doses of a (non-clozapine) atypical antipsychotic agent not be used instead of standard doses in patients with schizophrenia who inadequately respond to a standard-dose antipsychotic agent.* * Evidence was only available for use of high-dose risperidone and high-dose quetiapine. There were no studies comparing other atypical antipsychotic agents used at high doses with standard-dose (non-clozapine) antipsychotic therapy. Of note, the threshold for defining high-dose quetiapine in the CADTH systematic review was higher than Health Canada–approved doses.

Detailed information regarding these recommendations (i.e., vote results, the rating of overall quality of clinical evidence, underlying values and preferences related to the recommendations, clinical notes, and context) is provided in Appendix 2.

5.2 Research Gaps

An important aspect of CADTH's mandate includes the identification and dissemination of research gaps; that is, areas in which there is insufficient evidence to guide optimal prescribing and use. The following sections outline gaps in research related to combination and high-dose atypical antipsychotic treatment strategies in adolescents and adults with schizophrenia. Identification of these gaps will assist researchers and research funding organizations in planning future clinical research. The knowledge that results from such research will lead to improved clinical practice and better outcomes for patients with schizophrenia.

5.2.1 Populations, interventions, comparators, and outcomes with insufficient evidence

Only one study evaluating high-dose antipsychotics was identified in adolescent patients with schizophrenia inadequately controlled on standard-dose antipsychotics. No studies in this population were identified for combination therapies. Additionally, further research is required to identify subpopulations likely to experience greater benefits or greater risk of harm when using combination or high-dose AAP strategies. No studies were identified that analyzed subgroups of patients who were partial responders to baseline therapy.

Patients with treatment-resistant schizophrenia are defined as patients who had limited or no response (based on Positive and Negative Symptoms Scale [PANSS] or Brief Psychiatric Rating Scale [BPRS] scores) or intolerance to two to three antipsychotics with dosing up to manufacturer's maximum recommended dose.[13] The study level definitions of inadequate control of schizophrenia were mostly based on Kane's criteria[13] or with some modification, but some studies did not explicitly define inadequate control or intolerance.

There was insufficient evidence for a number of outcomes considered important for making recommendations on the use of combination and high-dose AAP therapies. In particular, insufficient evidence was available for mortality, hospitalizations, relapse rates, suicidality, health-related quality of life, level of function, and long-term adverse effects of combination or high-dose antipsychotic use. Available trials were underpowered for any meaningful evaluation of safety. Longer trials powered to detect these outcomes are required, to provide more definitive information regarding the comparative clinical and economic benefits of combination or high-dose therapeutic strategies.

In terms of the comparisons conducted in studies, the majority compared clozapine (CLZ)-based combination therapy with CLZ monotherapy or high-dose non-CLZ AAP therapy with CLZ monotherapy. No trials compared non-CLZ-based AAP combinations therapies with CLZ monotherapy, and only one trial compared high-dose non-CLZ AAP therapy with the same AAP in a standard dose. Both of these comparisons are of relevance to clinicians. Additionally, no trials studied long-acting antipsychotic injections, either as part of a combination or high-dose strategy, or as a comparator to one. The research gaps identified in this review are summarized in Table 3.

Table 3: Populations, Interventions, and Outcomes Requiring Further Research

Category	Research Gap
Population	• Patients < 18 years of age • Subgroups likely to achieve greater benefit with combination or high-dose use • Subgroups at greater risk of harm with combination or high-dose use • Patients who are partial responders to standard-dose AAP monotherapy
Interventions and Comparators	• Comparisons between non-CLZ combinations and CLZ monotherapy • Comparisons between high-dose non-CLZ AAP therapy and the same AAP in standard dose • Long-acting (injectable) antipsychotic agents

Table 3: Populations, Interventions, and Outcomes Requiring Further Research	
Category	**Research Gap**
Outcomes	• Mortality • Hospitalizations • Suicidality • Relapse rate • Health-related quality of life • Level of function • Long-term adverse effects of high-dose or combination APD use

AAP = atypical antipsychotics; APD = antipsychotic drugs; CLZ = clozapine.

6 THE EVIDENCE

The clinical evidence for the use of AAP combination and high-dose treatment strategies in adolescents and adults with schizophrenia inadequately controlled on standard-dose monotherapy was derived from the CADTH Optimal Use Report: *A Systematic Review of Combination and High-Dose Atypical Antipsychotic Therapy in Patients with Schizophrenia*.[14] A cost-effectiveness analysis based upon the results of the systematic review was originally planned. However, in consultation with CERC, it was determined that such an analysis would be of limited utility, given the lack of consistent differences in efficacy and safety between high-dose and combination treatment strategies and standard-dose antipsychotic monotherapy. Hence, the cost information provided for CERC's deliberations consisted of the acquisition costs for the various treatment strategies considered (Appendix 3).

7 CONSIDERATION OF THE EVIDENCE

7.1 COMPUS Expert Review Committee Process and Perspective

CERC members consider clinical effectiveness (i.e., benefits and harms), burdens, and cost data when formulating Optimal Use Recommendations. Committee members bring their individual expertise and experience to bear (as experts, general practitioners, interventionists, consumers, members of the public) and draw upon their own values and preferences to discuss the evidence and reach conclusions.

CERC develops recommendations and advice with the aim of contributing to optimal health outcomes and fostering a sustainable health care system for Canadians. CERC considers the practical needs of policy-makers, health care providers, and consumers in implementing and using the recommendations and advice toward the promotion of optimal practices. To assist in knowledge transfer to intended audiences, CERC also develops Context Statements (where appropriate) to provide guidance based on clinical judgment where there is insufficient evidence, and to provide commentary relating to the evidence.

8 NEXT STEPS

The Optimal Use Recommendations will be widely disseminated to encourage uptake and implementation by decision-makers at various levels (e.g., policy decision-makers, health care professionals, and patients). Gaps in practice and knowledge related to the use of atypical antipyschotic drugs will be identified by comparing the final recommendations with information on current practice[15] and utilization[16] of these products in Canada.

Key messages to promote the optimal prescribing and use of atypical antipsychotics will be developed to address identified gaps in practice and knowledge. Intervention tools will be populated with the key messages and related evidence for implementation across Canada.

APPENDIX 1: EXPERT COMMITTEE AND CONTRIBUTORS

COMPUS (Canadian Optimal Medication Prescribing and Utilization Service) Expert Review Committee (CERC)

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Conflicts of Interest

Dr. Michael Evans has received grant support from AstraZeneca Canada Inc. to offset the cost of Mini Medical School, an educational program for the public.

Dr. Scott Klarenbach is a member of a research group funded by an unrestricted grant to the Alberta Kidney Disease Network from Amgen Canada Inc. and Merck Frosst Canada Ltd.

Dr. Richard Williams has received funding for educational lectures from Eli Lilly and funding for conferences from Pfizer. He has received compensation for consulting services from Bristol-Myers Squibb Canada. He has received compensation for consulting services and research funding from Organon Canada Ltd., Janssen-Ortho Inc., Pfizer, Eli Lilly, and AstraZeneca Canada. He has received research funding from Obecure, Sanofi-aventis Canada, and Solvay.

Dr. Gary Remington has received financial support for his research from Novartis Canada, Medicure, and Merck KGaA (Germany). He is also involved in a phase 1 clinical trial with Neurocrine Biosciences.

Dr. Heather Milliken has received funding for educational lectures and compensation for consulting services from Pfizer and Janssen-Ortho Inc. She has also received research funding from Janssen-Ortho Inc. and Eli Lilly.

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APPENDIX 2: DETAILED RECOMMENDATION AND SUPPORTING EVIDENCE

Background

The detailed recommendation tables offer the following information:

- **Vote results —** Indicates the number of COMPUS (Canadian Optimal Medication Prescribing and Utilization Service) Expert Review Committee (CERC) members voting in favour of the proposed recommendation statement.

- **Underlying values and preferences —** Indicates the values and preferences that CERCmembers identified as most important in guiding the recommendation.

- **Clinical notes —** Provides guidance from CERC regarding specific clinical considerations that may assist patients, policy decision-makers, and clinicians in selecting optimal use, especially in areas where there is a lack of sufficient evidence.

- **Context —** Lists key points arising from CERC members' deliberation of the evidence pertaining to the recommendation. This information is provided to assist patients, clinicians, and policy decision-makers with the interpretation and application of the recommendation and underlying evidence.

- **Evidence —** The most pertinent evidence used in generating the recommendations is presented following each recommendation.

Optimal Use Recommendation 1: Clozapine Combinations versus Monotherapy

CERC recommends that clozapine-based antipsychotic combination therapy should not be used for patients with schizophrenia who inadequately respond to standard-dose clozapine monotherapy.*

(Voting: agree 9; disagree 0)

* The available data for combination therapy with clozapine were primarily for oral risperidone, with some evidence available for aripiprazole and sulpiride. There was no evidence available for other atypical antipsychotic agents.

Underlying Values and Preferences

When developing this recommendation, CERC placed a high value on:

- The few significant differences in clinical efficacy between clozapine-based antipsychotic combination therapy and standard-dose clozapine monotherapy, and the lack of consistent evidence
- Safety concerns of augmenting clozapine treatment with an additional antipsychotic agent.

CERC also considered:

- The higher cost of adding another antipsychotic agent to clozapine.

Context

- With respect to the available evidence for this comparison, four CERC members considered the evidence to be of low quality, three of moderate quality, and one of high quality. The evidence pool consisted of 12 randomized controlled trials (RCTs; presented in 13 articles)[17-29] with three rated as being of good quality using the Scottish Intercollegiate Guidelines Network (SIGN-50) rating scheme. Most studies tended to be short term and underpowered for clinically relevant outcomes.
- No clinically important benefits were seen with combination therapy, and there may be an increase in serious adverse effects and costs. A statistically significantly increased risk of serious adverse events was found with clozapine combination therapy compared with clozapine monotherapy. In the case of clozapine combined with risperidone, harms such as sinus tachycardia, severe psychotic disorder, and severe hallucinations were more prevalent in comparison with clozapine monotherapy.
- Despite not being recommended, for those patients who *are* initiated on clozapine-based combination therapy, clinical opinion suggests that efficacy should be evaluated after an adequate trial using therapeutic doses up to the maximum recommended doses. If no improvement is observed or adverse events become apparent, clozapine-based combination therapy should be discontinued.
- There was no RCT evidence available examining clozapine-based combination therapy involving more than two agents. Clinical opinion suggests that the risk of adverse events increases significantly as the number of antipsychotic agents used in combination increases.

Summary of Clinical Evidence

With respect to efficacy, the only statistically significant difference between treatments was in the Clinical Global Impression — Improvement scale (CGI-I), where a slightly greater improvement was seen in the clozapine (CLZ) combination arm compared with CLZ monotherapy at the end of 16 weeks' treatment. The risk of serious or severe adverse events was significantly higher in the CLZ-combination arm versus CLZ monotherapy, although total cholesterol was slightly lower in the combination arm. There were no statistically significant differences between treatments for any other harms outcomes.

Table A1: Summary of Results from Reference Case Meta-analyses of Clozapine-Combination Therapy versus Clozapine Monotherapy

Outcome	No. Trials	No. Pts	Effect Estimate (95% CI)	Heterogeneity (I^2)
Efficacy Outcomes				
PANSS — total*§	4	327	Data not pooled due to high heterogeneity	N/A
PANSS — positive*‡	4	327	0.23 (-0.97 to 1.43)	75%
PANSS — negative*‡	4	327	-0.34 (-1.07 to 0.39)	26%
BPRS*§	2	114	-0.88 (-4.32 to 2.55)	56%
CGI-I*§	1	206	-0.30 (-0.58 to -0.02) (WMD at end point)	N/A
CGI-S*‡	5	424	0.04 (-0.22 to 0.30)	63%
GAF*§	2	236	-1.43 (-6.28 to 3.42)	66%
QOL scale*§	1	30	0.30 (-5.93 to 6.53)	N/A
Response rate†‡	6	426	1.35 (0.81 to 2.25)	0%
Harms				
AIMS*‡	3	107	0.02 (-0.77 to 0.80)	38%
BARS*§	3	107	-0.29 (-0.79 to 0.20)	51%
SAS*§	4	314	-0.25 (-0.72 to 0.22)	15%
Akathisia†§	3	251	3.41 (0.46 to 25.44)	0%
Cholesterol — total*‡ (mmol/L)	3	307	-0.15 (-0.25 to -0.06)	0%
EPS (number of pts with EPS)†§	2	235	2.25 (0.73 to 6.94)	N/A
EPS score (ESRS-T, DIEPSS)*§	2	130	0.18 (-0.77 to 1.13)	0%
Hospitalization†§	1	68	3.00 (0.13 to 71.15)	N/A
Mortality (all-cause) †§	1	207	Not estimable	N/A
Parkinsonism†§	2	41	0.60 (0.08 to 4.54)	N/A

Table A1: Summary of Results from Reference Case Meta-analyses of Clozapine-Combination Therapy versus Clozapine Monotherapy				
Outcome	**No. Trials**	**No. Pts**	**Effect Estimate (95% CI)**	**Heterogeneity (I^2)**
Serious/severe adverse events†§	6	410	8.45 (1.03 to 69.54)	0%
Weight gain (number of pts with weight gain) †‡	3	285	0.65 (0.16 to 2.61)	0%
Withdrawals (all-cause) †§	8	503	1.30 (0.78 to 2.17)	0%
Withdrawals due to adverse events†§	5	380	1.68 (0.49 to 5.75)	0%

AIMS = Abnormal Involuntary Movement scale; BARS = Barnes Akathisia Rating Scale; BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impression — Improvement scale; CGI-S = Clinical Global Impression — Severity scale; CI = confidence interval; DIEPSS = Drug-Induced Extrapyramidal Symptoms Scale; EPS = extrapyramidal symptoms; ESRS-T = Extrapyramidal Symptoms Rating Scale total score; GAF = Global Assessment of Functioning; N/A = not applicable; PANSS = Positive and Negative Symptom Scale; QOL = quality of life; SAS = Simpson-Angus Scale; WMD = weighted mean difference.

* WMD of change from baseline for combination minus monotherapy.
† Risk ratio (combination/monotherapy) for experiencing one or more events.
‡ Outcome was ranked a priori by CERC as "important" to making a recommendation.
§ Outcome was ranked a priori by CERC as "critical" to making a recommendation.
For complete results, see CADTH Optimal Use Report: *A Systematic Review of Combination and High-Dose Atypical Antipsychotic Therapy in Patients with Schizophrenia*.[14]

Optimal Use Recommendation 2: Combination Therapy with Non-clozapine Atypical Antipsychotic Agents versus Monotherapy

CERC recommends that non–clozapine-based atypical antipsychotic combination therapy should not be used for patients with schizophrenia who inadequately respond to a standard-dose atypical antipsychotic agent.*

(Voting: agree 9; disagree 0)

* Evidence was only available for the combination of risperidone or quetiapine with aripiprazole. There was no evidence for other combinations involving atypical antipsychotic agents.

Underlying Values and Preferences

When developing this recommendation, CERC placed a high value on:

- Safety concerns of augmenting atypical antipsychotic treatment with an additional antipsychotic agent
- The potentially higher cost of non–clozapine-based combination therapy in comparison with standard-dose monotherapy.

CERC also considered:

- The few significant differences in clinical efficacy between non–clozapine-based antipsychotic combination therapy and standard-dose non-clozapine monotherapy.

Context

- Evidence was very limited for this comparison, as only one RCT[30] was identified; all CERC members agreed that the available evidence was of low quality.
- Although the evidence from the single RCT did not indicate that combination antipsychotic therapy was associated with a higher risk of adverse effects than monotherapy, clinical experience and non-RCT evidence outside the scope of the CADTH review suggests that there are increased adverse effects associated with non–clozapine-based antipsychotic combination therapy.[31-33]

Summary of Clinical Evidence

There were no statistically significant differences between treatments for any efficacy-related outcomes for this comparison. In terms of harms, the only statistically significant differences were for prolactin and serious adverse events; for both outcomes, differences were in favour of combination therapy.

Table A2: Summary of Results for Combination Non-clozapine Atypical Antipsychotic Therapy with Atypical Antipsychotic Monotherapy

Outcome	No. Trials	No. Pts Analyzed	Effect Estimate (95% CI)
Efficacy			
PANSS — total*§	1	310	-0.10 (-2.59 to 2.79)
PANSS — positive*‡	1	310	0.50 (-0.40 to 1.40)
PANSS — negative*‡	1	310	0.10 (-0.84 to 1.04)
CGI-I*§	1	310	-0.10 (-0.38 to 0.18) (WMD at the endpoint)
CGI-S*‡	1	310	-0.00 (-0.19 to 0.19)
Quality of life*§	1	310	-1.10 (-4.06 to 1.86)
Response rate†‡	1	310	1.01 (0.78 to 1.33)
Harms			
Akathisia†§	1	322	0.82 (0.36 to 1.88)
Cholesterol — total*‡ (mmol/L)	1	253	-0.05 (-0.13, 0.03)
EPS (number of pts with EPS)†§	1	322	0.67 (0.35 to 1.28)
Prolactin (ng/mL)*‡	1	175	-10.40 (-16.53 to -4.27)
Mortality (all-cause)†§	1	322	Not estimable
Serious/severe adverse events†§	1	323	0.38 (0.17 to 0.85)
Suicide (completed) †§	1	322	Not estimable
Suicide (attempted) †§	1	322	0.30 (0.01 to 7.36)
Suicidal ideation†§	1	322	0.08 (0.00 to 1.48)
Weight gain (number of pts with weight gain) †‡	1	323	1.41 (0.77, 2.61)
Withdrawals (all-cause) †§	1	323	1.02 (0.74 to 1.41)
Withdrawals due to adverse events†§	1	323	0.51 (0.23 to 1.12)

CGI-I = Clinical Global Impression — Improvement scale; CGI-S = Clinical Global Impression — Severity scale; CI = confidence interval; EPS = extrapyramidal symptoms; PANSS = Positive and Negative Symptom Scale; pts = patients; WMD = weighted mean difference.

* Mean difference of change from baseline for combination minus monotherapy.
† Risk ratio (combination/monotherapy) for experiencing one or more events.
‡ Outcome was ranked a priori by CERC as "important" to making a recommendation.
§ Outcome was ranked a priori by CERC as "critical" to making a recommendation.

For complete results, see CADTH Optimal Use Report: *A Systematic Review of Combination and High-Dose Atypical Antipsychotic Therapy in Patients with Schizophrenia*.[14]

Optimal Use Recommendation 3: Standard-Dose Clozapine versus High-Dose Non-clozapine Atypical Antipsychotic Agents

CERC recommends that standard-dose clozapine should be used instead of high doses of other atypical antipsychotic agents for patients with schizophrenia who inadequately respond to a standard-dose atypical antipsychotic agent.*

(Voting: agree 8; disagree 1)

* Evidence was only available for use of high-dose risperidone and high-dose olanzapine. There were no studies comparing other atypical antipsychotic agents used at high doses with standard-dose clozapine. Of note, the threshold for defining high-dose olanzapine in the CADTH systematic review was higher than Health Canada–approved doses.

Underlying Values and Preferences

When developing this recommendation, CERC considered:

- Safety concerns related to use of high-dose risperidone or olanzapine compared with standard-dose clozapine, despite the lack of clear differences in safety profile between treatments in the available studies
- Clinical experience grounded in evidence beyond the scope of the CADTH systematic review indicating the higher efficacy of clozapine compared with other antipsychotic agents in the management of patients with treatment-resistant schizophrenia
- The inconsistent differences in clinical efficacy between high-dose risperidone and standard-dose clozapine, and the lack of consistent clinical evidence
- The fact that the cost of clozapine is higher than that of (generic) risperidone and other atypical antipsychotic agents used at high doses.

Context

- All CERC members rated the evidence as being of low quality. The evidence pool for risperidone consisted of three RCTS;[34-36] most were of short duration, and none were considered to be of high quality based on the SIGN-50 rating scheme. In terms of efficacy outcomes, standard-dose clozapine was statistically superior to high-dose risperidone for BPRS, CGI-S, extrapyramidal effects, and level of function (GAF); however, there was no difference in terms of PANSS or response rates. In terms of harms, high-dose risperidone was statistically superior in terms of Parkinsonism and weight. The clinical significance of these differences is uncertain.
- The evidence for olanzapine consisted of five RCTs,[35,37-40] none of which were considered to be of high quality, based on the SIGN-50 instrument. There were no statistically significant differences in efficacy outcomes between high-dose olanzapine and standard-dose clozapine. However, high-dose olanzapine was associated with a lower risk of withdrawal due to adverse events.
- It was unclear whether patients included in the available RCTs had previously achieved partial response on standard doses of antipsychotic agents. Furthermore, not all studies reported the number of antipsychotic agents that were previously tried. CERC noted that

most patients who have failed more than two agents in clinical practice move to standard-dose clozapine as the next treatment strategy.

- In some of the included studies, the daily dose of clozapine was considered suboptimal (< 350 mg per day).[36,38,40] However, comparison of trials with suboptimal clozapine dosing versus adequate dosing did not reveal a systematic difference in results. In the subgroup analysis of trials with mean clozapine doses above 350 mg per day, there were no significant differences in efficacy between clozapine and high-dose strategies, and a non-statistically significant trend toward more withdrawals due to adverse events in the clozapine arm.
- The CADTH review considered risperidone doses over 6 mg per day as high dose (based on expert opinion), while Health Canada has approved doses up to and including 12 mg per day. The average dose for risperidone in the included trials for this comparison was approximately 8 mg per d. For olanzapine, doses above 20 mg per day (the Health Canada–approved maximum recommended dose) were considered high in the CADTH review; the average dose in the included trials was approximately 32 mg per day.
- The daily cost of clozapine is higher than high-dose risperidone. The cost-effectiveness of clozapine compared with high-dose strategies is uncertain, as there was insufficient evidence on rehospitalizations and other clinically relevant outcomes related to health care utilization.
- Based on the available evidence (outside the scope of the CADTH review) demonstrating the higher efficacy of clozapine compared with standard doses of other antipsychotic agents,[38,41-43] most, but not all, CERC members considered standard-dose clozapine to represent the standard of care for patients with treatment-resistant schizophrenia. Although there were few statistically significant differences favouring clozapine over high-dose risperidone or olanzapine in the CADTH review, this evidence was considered insufficient to support the use of high-dose atypical antipsychotic agents in place of clozapine.

Summary of Clinical Evidence

There were no statistically significant differences in efficacy between treatments except for GAF scores, which were higher for standard-dose CLZ, and BPRS, which also saw greater improvement with standard-dose CLZ. With respect to harms, there were no statistically significant differences between groups for the majority of outcomes. The exceptions were a lower risk of extrapyramidal symptoms with clozapine, and fewer Parkinsonism events with high-dose risperidone.

Table A3: Summary of Results from Reference Case Meta-analyses of High-Dose Risperidone versus Standard-Dose Clozapine

Outcome	No. Trials	No. Pts	Effect Estimate (95% CI)	Heterogeneity (I^2)
Efficacy				
PANSS — total*§	3	323	3.60 (–4.52 to 11.71)	65%
PANSS — positive*‡	3	323	0.92 (–1.55 to 3.38)	53%
PANSS — negative*‡	3	323	1.25 (–0.18 to 2.68)	0%
BPRS*§	1	156	7.10 (3.65 to 10.55)	N/A
CGI-S*‡	2	242	0.40 (0.01 to 0.79)	68%
GAF*§	1	40	–7.50 (–12.83 to –2.17)	N/A
Response rate†‡	2	289	0.92 (0.74 to 1.15)	14%
Harms				
Agranulocytosis†§	2	329	0.17 (0.01 to 4.11)	0%
Cholesterol — total*‡ (mmol/L)	1	50	–0.18 (–0.85 to 0.49)	N/A
EPS (number of patients with EPS) †§	1	270	2.14 (1.29 to 3.56)	N/A
Mortality (all-cause) †§	1	273	1.02 (0.06 to 16.18)	N/A
Parkinsonism†§	1	86	0.63 (0.41 to 0.97)	0%
Suicide (completed) †§	1	86	Not estimable	N/A
Suicidal Ideation†§	1	86	1.00 (0.06 to 15.48)	N/A
Weight gain (number of pts with weight gain) †‡	1	86	0.63 (0.32 to 1.22)	0%
Withdrawals (all-cause) †§	3	420	0.96 (0.70 to 1.30)	0%
Withdrawals due to adverse events†§	3	420	0.74 (0.39 to 1.41)	0%

BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression — Severity scale; CI = confidence interval; EPS = extrapyramidal symptoms; GAF = Global Assessment of Functioning; N/A = not applicable; PANSS = Positive and Negative Symptom Scale; pts = patients; WMD = weighted mean difference.

* WMD of change from baseline for high dose minus standard dose.
† Risk ratio (high dose/standard dose) for experiencing one or more events.
‡ Outcome was ranked a priori by CERC as "important" to making a recommendation.
§ Outcome was ranked a priori by CERC as "critical" to making a recommendation.
For complete results, see CADTH Optimal Use Report: *A Systematic Review of Combination and High-Dose Atypical Antipsychotic Therapy in Patients with Schizophrenia*.[14]

There was no statistically significant difference in efficacy outcomes between high-dose olanzapine and standard-dose clozapine. However, high-dose olanzapine was associated with a lower risk of withdrawal due to adverse events.

Table A4: Summary of Results from Reference Case Meta-analyses of High-Dose Olanzapine versus Standard-Dose Clozapine

Outcome	No. Trials	No. Pts	Effect Estimate (95% CI)	Heterogeneity (I^2)
Efficacy				
PANSS — total*§	4	367	0.84 (–5.31 to 7.0)	59%
PANSS — positive*‡	4	367	0.71 (–1.00 to 2.43)	32%
PANSS — negative*‡	4	367	Data not pooled due to high heterogeneity	N/A
BPRS*§	1	180	–1.20 (–5.43 to 3.03)	N/A
CGI-S*‡	3	288	–0.02 (–0.39 to 0.34)	30%
GAF	No data			
Response rate†‡	2	216	1.05 (0.83 to 1.33)	0%
Harms				
Agranulocytosis†§	1	40	0.38 (0.04 to 3.56)	N/A
Cholesterol — total*‡ (mmol/L)	3	152	–0.15 (–0.52 to 0.22)	5%
EPS (number of patients with EPS) †§	1	57	2.56 (0.39 to 16.67)	N/A
Mortality (all-cause) †§	No data			
Parkinsonism†§	1	176	0.76 (0.30 to 1.95)	0%
Suicide (completed) †§	No data			
Suicidal ideation†§	No data			
Weight gain (number of pts with weight gain)† ‡	2	237	0.85 (0.36 to 2.03)	0%
Withdrawals (all-cause) †§	5	250	0.96 (0.69 to 1.32)	33%
Withdrawals due to adverse events†§	4	310	0.36 (0.15 to 0.85)	0%

BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression — Severity scale; CI = confidence interval; EPS = extrapyramidal symptoms; GAF = Global Assessment of Functioning; N/A = not applicable; PANSS = Positive and Negative Symptom Scale; pts = patients; WMD = weighted mean difference.

* WMD of change from baseline for high dose minus standard dose.
† Risk ratio (high dose/standard dose) for experiencing one or more events.
‡ Outcome was ranked a priori by CERC as "important" to making a recommendation.
§ Outcome was ranked a priori by CERC as "critical" to making a recommendation.
For complete results, see CADTH Optimal Use Report: *A Systematic Review of Combination and High-Dose Atypical Antipsychotic Therapy in Patients with Schizophrenia*.[14]

Optimal Use Recommendation 4: Standard-Dose versus High-Dose Non-clozapine Atypical Antipsychotic Agents

CERC recommends that high doses of a (non-clozapine) atypical antipsychotic agent not be used instead of standard doses in patients with schizophrenia who inadequately respond to a standard-dose antipsychotic agent.*

(Voting: agree 9; disagree 0)

* Evidence was available only for use of high-dose risperidone and high-dose quetiapine. There were no studies comparing other atypical antipsychotic agents used at high doses with standard-dose (non-clozapine) antipsychotic therapy. Of note, the threshold for defining high-dose quetiapine in the CADTH systematic review was higher than Health Canada–approved doses.

Underlying Values and Preferences

When developing this recommendation, CERC placed a high value on:

- The few significant differences in clinical efficacy between high-dose risperidone or quetiapine and standard-dose atypical antipsychotics, and the lack of consistent evidence
- Safety concerns regarding using high-dose antipsychotic therapy
- The higher costs of high-dose antipsychotics in comparison with standard doses.

Context

- In the CADTH systematic review, studies comparing high-dose AAPs with typical antipsychotic agents were included regardless of the dose of the typical antipsychotic. The typical antipsychotics used as comparator in the identified trials were haloperidol[35,44-48] and chlorpromazine.[49] Based on clinical opinion, CERC considered haloperidol 10 mg and chlorpromazine 1,000 mg to be the maximum daily doses in clinical practice; studies that used higher doses were not considered. Hence, the evidence considered by CERC in developing this recommendation consisted of one study comparing high-dose risperidone with haloperidol 10 mg per day,[48] and one study comparing high-dose quetiapine with standard-dose quetiapine.[50]
- Eight CERC members considered the quality of evidence to be of low quality, and one, moderate quality. Neither of the included studies was rated as being of high quality according to the SIGN-50 rating scheme. There was a lack of evidence for many clinically important endpoints such as relapse, hospitalizations, mortality, functional capacity, and clinical remission.
- It was unclear whether patients included in the available RCTs had previously achieved partial response on standard doses of antipsychotic agents.

Summary of Clinical Evidence

With respect to efficacy, there were no statistically significant differences between treatments. There were no statistically significant differences between groups for the majority of harms outcomes.

Table A5: Summary of Results from Reference Case Meta-analyses of High-Dose Non-clozapine Atypical Antipsychotics versus Standard-Dose Non-clozapine Antipsychotic Drugs

Outcome	No. Trials	No. Pts	Effect Estimate (95% CI)	Heterogeneity (I^2)
Efficacy				
PANSS — total*§	2	175	Data not pooled due to high heterogeneity	N/A
PANSS — positive*‡	2	175	Data not pooled due to high heterogeneity	N/A
PANSS — negative*‡	2	175	–0.13 (–1.12 to 0.86)	0%
CGI-S*‡	1	131	–0.10 (–0.61 to 0.41)	NA
Response rate†‡	2	175	1.27 (0.65 to 2.47)	44%
Harms				
Cholesterol — total (mmol/L)*‡	1	131	0.08 (–0.19 to 0.35)	NA
EPS (number of patients with EPS) †§	2	175	0.70 (0.27 to 1.19)	0%
Mortality (all-cause)†§	1	131	Not estimable	N/A
Serious/severe adverse events†§	1	131	1.47 (0.16 to 13.68)	N/A
Suicide (completed)†§	1	131	Not estimable	N/A
Suicide (attempted)†§	1	131	Not estimable	N/A
Suicidal ideation†§	1	131	1.49 (0.06 to 37.37)	N/A
Tardive dyskinesia†§	1	131	0.16 (0.02 to 1.52)	N/A
Weight gain (number of pts with weight gain)†‡	1	131	4.40 (0.58 to 33.60)	N/A
Withdrawals (all-cause)†§	2	173	0.64 (0.11 to 3.60)	63%
Withdrawals due to adverse events†§	2	173	1.09 (0.27 to 4.42)	0%

CGI-S = Clinical Global Impression — Severity scale; CI = confidence interval; EPS = extrapyramidal symptoms; N/A = not applicable; PANSS = positive and negative symptom scale; pts = patients; WMD = weighted mean difference.

* WMD of change from baseline for high dose minus standard dose.
† Risk ratio (high dose/standard dose) for experiencing one or more events.
‡ Outcome was ranked a priori by CERC as "important" to making a recommendation.
§ Outcome was ranked a priori by CERC as "critical" to making a recommendation.
For complete results, see CADTH Optimal Use Report: *A Systematic Review of Combination and High-Dose Atypical Antipsychotic Therapy in Patients with Schizophrenia*.[14]

APPENDIX 3: ATYPICAL ANTIPSYCHOTIC COSTING INFORMATION

The table below outlines the representative wholesale daily costs for standard-dose, high-dose, and combination AAP therapy. Average doses were obtained from trials included in the systematic review in all cases except for combination strategies, for which standard doses of each agent were assumed. The cost information for clozapine is extracted from the Saskatchewan public drug plan, and all other costs are from the Ontario public drug plan. The combinations of agents and high doses listed in this table are provided as examples and are not approved by Health Canada.

Treatment Strategies	Dose (mg/d)	Daily cost ($)
Clozapine monotherapy	400	10.56
Clozapine high dose	600	15.84
Olanzapine monotherapy	20	3.58
Olanzapine high dose	30	5.37
Risperidone monotherapy	4	1.21
Risperidone high dose	8	2.42
Quetiapine monotherapy	700	2.31
Quetiapine high dose	1100	3.63
Olanzapine + Risperidone	OLZ 20; RIS 4	Total: 7.70 OLZ/RIS: 3.58/1.21
Aripiprazole + Ziprasidone	ARI 15; ZIP 100	Total: 8.04 ARI/ZIP – 4.50/3.54
Quetiapine + Risperidone	Quet 600; RIS 4	Total: 3.19 QUET/RIS: 1.98/1.21
Clozapine+Aripiprazole	CLZ 400; ARI 15	Total: 15.06 CLZ/ARI: 10.56/4.50

CLZ = clozapine; OLZ = olanzapine; QUET = quetiapine; RIS = risperidone; ZIP = ziprasidone.

APPENDIX 4: DETAILED COMPUS EXPERT REVIEW COMMITTEE PROCESS

The steps that CERC followed for generating Optimal Use Recommendations are presented here. A modified Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework was used to develop the recommendations. More details regarding the CERC process can be found in the project protocol.

1. Individual review of clinical evidence and provision of initial feedback
CERC members were provided with the clinical and cost evidence as a draft scientific report. Members completed a form designed to elicit feedback on the available evidence and its quality, their values and preferences, and possible recommendations, Clinical Notes, and Context Statements. Feedback was collated and provided to the committee.

2. Preparatory work prior to the identification of draft Optimal Use Recommendations
CERC members discussed via teleconference the clinical and cost evidence presented, as well as the collated feedback from individual members. Discussions involved dialogue on the quality of evidence, benefits, harms or burdens, and cost implications.

3. Identification of draft Optimal Use Recommendations
At the face-to-face meeting to develop draft Optimal Use Recommendations, CERC continued discussion on the collated comments from the feedback form along with new input. Any outstanding issues with respect to the evidence, values and preferences, or other considerations were clarified. CERC then proceeded to vote on the following items (in the order presented):

1) Overall quality of the available evidence: Possible ratings were "high," "moderate," and "low." This rating was based on an assessment of evidence quality across all outcomes considered "important" or "critical" by CERC. Where evidence was lacking for such outcomes, an overall rating of "low" was more likely, regardless of the quality of evidence for outcomes reported in studies.

2) Identification of values and preferences: Members were asked to identify the two most important values and preferences underlying their recommendation on the use of atypical antipsychotic combination therapy and high-dosing treatment strategies in adolescents and adults with schizophrenia inadequately controlled on standard-dose monotherapy.

4. Voting on the draft Optimal Use Recommendation
Once a draft recommendation was developed based on the committee's deliberations, CERC members voted on the recommendation. Voting was conducted by secret ballot. Quorum consisted of a minimum of five core CERC members and 50% of the committee members appointed as clinical experts in the management of schizophrenia. A majority vote was sufficient for a draft recommendation to be accepted. Each vote concluded with a committee discussion on the vote results in which members were given an opportunity to discuss factors behind their individual votes. Clinical Notes and Contextual statements around the recommendations were also discussed, to capture issues and areas of discussion not covered within the recommendation. Draft Optimal Use Recommendations could be edited by CERC during these deliberations; however, a revote was required for substantial changes.
5. Identification of research gaps

Where there was insufficient information available when drafting Optimal Use Recommendations, CERC identified "gaps" in research and knowledge. These consisted of populations, treatment comparisons, and outcomes of clinical interest for which evidence was insufficient.

APPENDIX 5: ABBREVIATIONS

AAP	atypical antipsychotic
ACP	Advisory Committee on Pharmaceuticals
BPRS	Brief Psychiatric Rating Scale
CAC	COMPUS Advisory Committee
CADTH	Canadian Agency for Drugs and Technologies in Health
CERC	COMPUS Expert Review Committee
CGI-S	Clinical Global Impressions — Severity scale
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
DPAC	Drug Policy Advisory Committee
DSM-IV TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
OUWG	Optimal Use Working Group
PANSS	Positive and Negative Syndrome Scale
RCT	randomized controlled trial
SAS	Simpson-Angus Scale
SIGN	Scottish Intercollegiate Guidelines Network

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