Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

Optimal Use Report

CADTH

Volume 1, Issue 1D

August 2012

Optimal Use of Atypical Antipsychotics for Schizophrenia: Combination Therapy, High Doses, and Clozapine — Current Practice Study

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ISSN: 1927-0127

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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)
- 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 terms 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 (AAPs) 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]

2.2 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.

2.3 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 AAPs are of the second-generation antipsychotic class.

At the time the research was conducted, seven AAPs were available in Canada: aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. Two other AAPs, asenapine and iloperidone, were approved in the US, while sulpiride and amisulpride were available in the European Union (Table 1). Since the completion of the research, asenapine has become available in Canada.

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

Generic Name	Trade Name	Dose Range	Definition of High Dose*	Manufacturer
Aripiprazole	Abilify	10–15 mg/day	> 30 mg/day	Bristol-Myers Squibb
Asenapine†	Saphris	10 mg/day (5 mg b.i.d.)	> 10 mg/day	Schering-Plough
Clozapine	Clozaril	300–600 mg/day	> 600 mg/day‡	Novartis
Olanzapine	Zyprexa, Zyprexa Zydis	5–10 mg/day	> 20 mg/day	Eli Lilly
Olanzapine†§	Zyprexa Relprevv	150–300 mg/2 weeks	> 300 mg/ 2 weeks (405 mg/ 4 weeks)	Eli Lilly
Iloperidone†	Fanapt	12–24 mg/day (administered 6–12 mg, b.i.d.)	> 24 mg/day	Titan Pharmaceuticals
Paliperidone	Invega	6–12 mg/day	> 12 mg/day	Janssen-Ortho
Paliperidone injection§	Invega Sustenna	39–234 mg/month	> 234 mg/month	Janssen-Ortho

Table 1: List of Atypical Antipsychotics Available in Canada and the US (cont'd)				
Generic Name	**Trade Name**	**Dose Range**	**Definition of High Dose***	**Manufacturer**
Quetiapine	Seroquel	300–800 mg/day	> 800 mg/day	AstraZeneca
Quetiapine	Seroquel XR	400–800 mg/day	> 800 mg/day	AstraZeneca
Risperidone	Risperdal, Risperdal M-Tab	4–6 mg/day	> 6 mg/day[¶]	Janssen-Ortho
Risperidone injection[§]	Risperdal Consta	25–50 mg/2 weeks	> 50 mg/2 weeks	Janssen-Ortho
Ziprasidone	Zeldox	120–160 mg/day	> 160 mg/day	Pfizer

b.i.d. = twice daily.
[*] Based on maximum recommended doses according to the product monograph, unless otherwise indicated.
[†] Approved by the US Food and Drug Administration, but not available in Canada at the time of this research. Now available in Canada.
[‡] Based on expert opinion. Maximum recommended dose according to product monograph is 900 mg per day.
[§] Long-acting injectable agent
[¶] Based on expert opinion. Maximum recommended dose according to product monograph is 16 mg per day.

3 OBJECTIVE

The objective of this study was to explore the views and experiences of health care professionals with respect to the use of AAP combination therapy and high-dose treatment strategies in adolescents and adults with schizophrenia.

4 PROJECT OVERVIEW

Once a topic is selected, CADTH undertakes activities related to key areas in the procedure. DPAC and the OUWG provide advice and guidance throughout the process, from topic identification through to supporting intervention and evaluation tools. CERC provides expert advice and recommendations on the topic area relating to 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 Current Practice Analysis step toward identifying practice and knowledge gaps related to the prescribing and use of AAP therapy for schizophrenia.

5 RESEARCH QUESTIONS

1. What is the clinician's approach to prescribing atypical antipsychotic agents for adult patients with schizophrenia? What factors are considered when determining class of antipsychotic, optimal dosage, and combination therapy?
2. What is the clinician's approach to switching to a new treatment strategy upon relapse or suboptimal response to a treatment strategy? How is suboptimal response defined? When is a new treatment strategy initiated? What options are preferred at this stage: a switch to a new agent, increasing the dosage of the originally prescribed agent, or moving to combination therapy?

3. What is the clinician's approach to prescribing clozapine to adult patients with schizophrenia? Under what circumstances is a switch to clozapine considered? Is clozapine ever prescribed at higher-than-recommended dosage or as part of combination therapy?
4. Does the clinician's approach to prescribing atypical antipsychotics to adults with schizophrenia differ from his or her approach to adolescent patients with schizophrenia?
5. How does the clinician assess the current level of information available to him or her on the topics of atypical antipsychotics, dosages, combination therapy, and clozapine? What are the preferred sources of information on these topics?

These research questions formed the basis for the moderator's guide, which is presented in Appendix 2 of this report.

6 METHODS

CADTH retained Vision Research to develop research instruments, recruit participants, to moderate and report on a series of in-depth interviews designed to provide insight into current practices and decision-making processes used by physicians (both psychiatrists and family physicians with experience treating patients with schizophrenia) when prescribing and dosing AAP agents (including clozapine) for patients with schizophrenia. The study also explored the perceptions of physicians relative to the availability of clinical information and guidelines for AAP agents.

The research methodology involved a series of one-on-one, in-depth interviews over the telephone, with participants from a variety of provinces and territories (Table 2). This methodology proved to be convenient for participants (helping with recruitment) and allowed us to effectively recruit from among a wide population of psychiatrists in Canada, yielding rich qualitative data.

A single moderator's guide was developed for interviews with both family physicians and psychiatrists. The results for these two groups were analyzed and reported on separately, although important differences and similarities are noted in this report.

Samples of psychiatrists and family physicians were selected randomly from across Canada using commercially available lists, and subsequently screened for experience in treating schizophrenia. Consent for participation in the study was obtained and an honorarium was offered to each participant. Interviews were guided by experienced moderators and lasted approximately 40 minutes. No observers listened in on the conversations. All interviews were audio-recorded for analysis and reporting. The personal identity of participants was kept confidential at every stage of the research and all comments were kept anonymous.

Recruiters strove for a blend of women and men, and urban and rural practitioners. All interviews were conducted in English, although interview participants were given the option of conducting the interview in French.

Transcripts were analyzed, first using a qualitative content analysis approach, respecting the structure of questions as they appeared in the moderator's guide and the two groups of participants in the study: psychiatrists and family physicians. The content analysis of the transcripts noted the range of answers provided by participants and the extent of consensus and division with respect to key points. The results and findings are summarized in sections 7 and 8 of this report.

Next, the transcripts were analyzed using a thematic analysis approach to identify broad themes that cut across questions and participant groups. The results from this thematic analysis are summarized in section 7.

7 RESULTS

Interviews were conducted during October and November of 2010. A total of 36 interviews were conducted, all in English.

7.1 Psychiatrists

A total of 26 practising psychiatrists in Canada participated in interviews. A sample of actual responses is provided in Appendix 3 .

Table 2: Demographics of Participating Psychiatrists

Gender		Region			Setting		Practice		
Male	Female	BC, AB, SK, MB	ON, QC	Atlantic Canada	Urban	Rural	Solo	Group	Hospital
20	6	7	17	2	21	5	7	3	16

AB = Alberta; BC = British Columbia; MB = Manitoba; ON = Ontario; QC = Quebec; SK = Saskatchewan.

7.1.1 Prescribing atypical antipsychotic agents for adults with schizophrenia

All psychiatrist participants indicated that they treat newly diagnosed patients with schizophrenia or psychosis and that they routinely prescribe AAPs. Most considered the side effect profile of this newer class of drugs as the principal advantage, particularly a lower risk of tardive dyskinesia (TD) and other extrapyramidal side effects (EPS). A substantial number of participants also pointed to advantages of AAPs in terms of clinical efficacy, including improvements to positive and negative symptoms, as well as mood stabilization. Other participants pointed to their own clinical experience with the drugs and the opinions of peers as motivating factors.

Nearly all respondents considered a number of factors when determining the optimal dosage for their adult patients with schizophrenia. The severity of symptoms presented by the patient and the patient's progress toward achieving remission were mentioned most often. Respondents also considered the side effects experienced by the patient when determining optimal dosage. A number of participants also considered the patient's demographic profile, in particular age, gender, and racial profile. Many also considered other, more individualized factors, such as metabolic issues, medical history, comorbidities, other medicines, and substance abuse. Finally, variables such as the cost of drugs, patient and family preferences, and medical literature were considered as part of a complex system of decision-making by some participants.

When judging whether initial treatment is effective, the majority of psychiatrists looked for a decrease in the psychotic symptoms presented by the patient as the chief criterion. A number of participants also looked for improvements in the overall functioning of the patient, such as the ability to socialize or return to work. A smaller number of participants also considered the side effects experienced by the patient when judging the effectiveness of the initial therapy.

Participants varied in the time they allowed to determine whether a treatment strategy was effective. A small number indicated that they looked for signs of improvement quickly — within 10 days to two weeks — whereas others looked for improvement over four to eight weeks. Many respondents tailored their approach to each individual patient, considering factors such as whether the patient was hospitalized, as well as the severity of symptoms and side effects.

A majority of participants went above the recommended dose for certain AAP agents before deciding to change their treatment strategy. A small number indicated that they rarely, if ever, exceeded the recommended dose. Most participants considered the side effects experienced by the patient when determining whether or not to exceed the recommended dosage before switching to a different agent.

The majority of psychiatrists rarely, if ever, used a combination of AAP agents as initial therapy, citing disadvantages both for the patient (e.g., increased risk of side effects, reduced adherence) and for the practitioner (e.g., lack of evidence on combination therapy, difficulty in pinpointing the cause of side effects). Those participants who have opted for combination therapy as initial therapy most often considered the sedating effects of certain agents (e.g., quetiapine) as beneficial for certain patients.

7.1.2 Treatment strategies upon suboptimal response or relapse

The majority of psychiatrists indicated that fewer than half their patients experienced a relapse or suboptimal response on recommended doses of multiple AAPs used as monotherapy. Experiences varied considerably, however, influenced by the practice setting. Work in emergency rooms (ERs) or hospitals predisposed participants to dealing with patients more likely to relapse. Participants also suggested that the more chronic cases are at greater risk of relapse or suboptimal outcomes.

Many participants indicated that their approach to relapse or suboptimal response included adjustment of the dose of the agent (even to beyond the recommended dose), switch to a new antipsychotic agent (other than clozapine) altogether, addition of a second antipsychotic agent, or switch to clozapine. The strategy adopted reflects both the clinician's individual preference and experience and, more importantly, the specific circumstances of the patient.

The approach to dealing with suboptimal response most often cited by participants was to stay with monotherapy and increase the dose, so long as some improvement in symptoms and function occurred and side effects remained tolerable. Four atypical antipsychotic agents were most likely to be prescribed at higher-than-recommended doses: olanzapine (Zyprexa), quetiapine (Seroquel), and, to a lesser extent, risperidone (Risperdal) and ziprasidone (Zeldox). For these agents, many participants tended to rely on their own clinical experience and that of their peers in determining the maximum dose they were willing to attempt for a given patient. Indeed, some respondents admitted to not knowing the maximum recommended doses for some of these agents. Participants were less likely to prescribe newer drugs at higher-than-recommended doses, due to the lack of clinical experience and evidence to determine safe levels.

Participants also considered the options of moving to combination therapy, or switching to a new agent altogether — including clozapine — with most basing the selection on the particular circumstances of the patient. Combinations were created to complement one another, so that weaknesses of the first agent were compensated for by the strengths of a second. The agent

most likely to be combined with others was quetiapine, selected for its ability to calm and sedate patients in addition to its antipsychotic properties. Bridging (i.e., tapering down of the existing medication while a new medication is titrated up) was also cited as a situation in which combinations are used.

7.1.3 Prescribing clozapine

The majority of psychiatrists had prescribed clozapine, although the percentage of patients taking clozapine varied greatly from one practitioner to another, ranging from less than 5% to 30%. A small number of psychiatrists did not prescribe clozapine themselves, instead referring to a more specialized practitioner. Some respondents felt that clozapine was underutilized.

The majority of participants prescribed clozapine to adult patients with schizophrenia after two or three optimized trials of other agents (both typical and atypical) had not yielded a good response, or had been discontinued due to side effects. Interestingly, most respondents indicated that there was good evidence regarding the superiority of clozapine for patients resistant to other antipsychotic agents. Other perceived advantages included effectiveness among suicidal patients, decreased substance abuse, and mood stabilization.

The chief disadvantages of clozapine cited by psychiatrists were the risk of agranulocytosis and the accompanying need for regular blood testing. Other side effects such as weight gain, metabolic side effects, cardiac problems, sedation, and seizures experienced by patients on clozapine were also considered. Perceived disadvantages for the care provider included long trial periods and the administrative burden of initiating the drug. Some also expressed concern that patients would not adhere to the regular monitoring that was required, thereby increasing the risk of agranulocytosis, while others indicated that patients were often reluctant to initiate clozapine due to its adverse effects profile and monitoring requirements. The majority of psychiatrists did not exceed the recommended dose of clozapine for their adult patients with schizophrenia, preferring instead to combine clozapine with another antipsychotic agent, especially risperidone or quetiapine if monotherapy with clozapine did not address all of the patient's symptoms. The small number of participants who did exceed the recommended dose of clozapine did so for patients with severe symptoms who were not improving.

7.1.4 Differences when treating adolescents with schizophrenia

The majority of psychiatrists indicated that they "rarely" or "occasionally" treated adolescents with schizophrenia, many of these on an emergency basis. Some participants did not treat adolescent patients at all.

Psychiatrists were just as likely or more likely to turn to AAP agents for adolescent patients as for adults, given the perception that typical agents were associated with a higher risk of adverse effects. Generally speaking, they considered similar factors as for adults in determining the optimal dose for adolescents, with the major difference being a more "conservative" approach overall ("low and slow"). Nearly all participants indicated that their approaches to combination therapy were no different for adolescent patients with schizophrenia than for adult patients.

Participants judged the effectiveness of treatment for adolescents and adults with schizophrenia in much the same way, with some suggesting they would allow more time before moving to a new treatment strategy, owing to greater concerns over side effects.

Most psychiatrists observed similar rates of relapse or suboptimal response among adolescent patients as adult patients. A small number felt relapse or suboptimal response was more likely among adolescents (perhaps related to substance abuse and lifestyle), while others felt these outcomes were less likely in adolescents.

Although the approach to combination therapy did not vary by age of the patient, the vast majority of respondents indicated they are reluctant to exceed the recommended dose with their adolescent patients. The approach to clozapine also differed by age, with the majority of participants indicating that they are less likely to prescribe clozapine to their adolescent patients, owing to concerns about side effects and inconvenience.

7.1.5 Assessment of information sources on atypical antipsychotic agents

Psychiatrists pointed to a lack of evidence-based guidelines to help guide their use of AAPs at higher-than-recommended doses. In the absence of such guidelines and evidence, psychiatrists relied on their own clinical experience and that of specialist colleagues in determining optimal and safe dosing of AAP agents.

Some participants felt there was evidence to guide the use of antipsychotic combination therapy, whereas a smaller number believed more evidence was needed. Psychiatrists generally felt there was adequate evidence to support the use of clozapine and guidelines for its use.

Psychiatrists called for more information on combination therapies involving mood stabilizers and studies focused on the efficacy and safety of new drugs and new combination therapies, as well as more information about the metabolic and side-effect profiles of typical and atypical agents.

Generally, most psychiatrists expressed a tendency to use multiple sources to gather information about AAP agents for patients with schizophrenia. Many preferred education events where specialists in the field of schizophrenic disorders presented cases and recommendations for treatment. Professional networks were also a key conduit for learning about and sharing best practices. Psychiatrists indicated they also turned to guidelines, journals, and other medical literature as other sources of information related to drug therapies for schizophrenia. Finally, a smaller number of psychiatrists also turned to pharmaceutical representatives and the literature they provide as important sources of information.

7.1.6 Results of thematic analysis

Analysis of the transcripts revealed some important themes that cut across most respondents and questions. A certain tension between evidence and clinical experience was evident in the decision-making process of psychiatrists when it comes to prescribing high doses and combinations of AAPs to patients with schizophrenia. Most participants acknowledged that there was little evidence to guide prescribing regarding these treatment strategies, and what evidence was available did not support combination and high-dose strategies. However, this contrasted with clinical experience (both their own and that of peers and opinion leaders), indicating that in some patients and in some situations, these strategies can be helpful. Participants described the need to resort to these strategies based on clinical judgment because of the potentially serious consequences of inadequately treated schizophrenia. However, a considerable degree of discomfort in employing high-dose and combination

strategies was evident in the responses, primarily due to the lack of evidence, insufficient guidance from existing guidelines, and the potential for severe toxicities.

Other themes that emerged were the importance of the relationships with the patient and family to successful therapy of schizophrenia. The psychiatrists with whom we spoke repeatedly stressed that their prescribing decisions are never taken in isolation but must be negotiated with family members (especially in the case of adolescents) and with the patients themselves; the nature of schizophrenia makes this negotiation and collaboration challenging. Unwillingness or inability to adhere to treatment was also cited as a major barrier. With respect to clozapine, participants described resistance from patients due to the adverse effect profile and requirements for regular blood testing. A related barrier was concern from psychiatrists that patients would not adhere to regular testing. Families were described as potential allies or barriers to treatment, as they often have considerable say in treatment decisions.

7.2 Family Physicians and General Practitioners

A total of 10 family physicians participated in interviews. Samples of their actual responses are provided in Appendix 4.

Table 3: Demographics of Participating Psychiatrists

Gender		Region			Setting		Practice		
Male	Female	BC, AB, SK, MB	ON, QC	Atlantic Canada	Urban	Rural	Solo	Group	Hospital
7	3	5	5	0	9	1	3	7	0

AB = Alberta; BC = British Columbia; MB = Manitoba; ON = Ontario; QC = Quebec; SK = Saskatchewan.

7.2.1 Prescribing atypical antipsychotic agents for adults with schizophrenia

All of the family physicians interviewed indicated they regularly treat adults with schizophrenia. Participants were unanimous in preferring the AAP agents over typical agents. Most cited both the effectiveness of the newer agents and the lower risk of side effects as the basis for this preference. One participant also cited “fast onset of action” as a reason for preferring atypical agents, and two participants introduced the notion of “comfort” with the atypical agents from long-term clinical experience. Interestingly, two participants indicated that they used both typical and atypical agents in their practice.

As with psychiatrists, family physicians considered the severity of symptoms and tolerability when determining optimal dose. Other factors were also considered, including cost, comorbidities, the patient’s age, and body weight.

Much like psychiatrists, family physicians looked for improvement in symptoms and, to a lesser extent, improvements in overall functioning, as indicators of a drug’s effectiveness. Some participants indicated they monitored side effects as well as effectiveness. Participants indicated they generally reassessed patients after two weeks to determine whether a change in treatment was required. The answers we received ranged from “a couple of days” to a month.

Family physicians did not typically exceed the maximum recommended dosage of antipsychotic agents. Most made it clear that they referred to a psychiatrist if it appeared the patient would need to exceed the maximum dose. Only one family physician was comfortable going "a little" above the maximum dose for AAP agents before then referring to a psychiatrist.

Participants did not typically use a combination of antipsychotic agents as initial therapy, citing lack of experience and comfort with this approach.

7.2.2 Treatment strategies upon suboptimal response or relapse

Family physicians varied somewhat when indicating what percentage of their patients experienced relapse or suboptimal response on recommended doses of multiple AAPs used as monotherapy. Most indicated that between 15% and 20% of patients relapse or have suboptimal response; one individual put the rate at 50%. As with the psychiatrists, many noted that success or failure is often a product of more than just drug efficacy, with adherence and support networks also playing an important role.

The majority of family physicians in this study indicated a preference for switching agents rather than increasing the dose beyond the recommended range, or beginning combination therapy. A small number indicated a preference for increasing the dosage if the response was suboptimal, but only if the patient was tolerating the drug well, and often with the assistance of a psychiatrist. Finally, some participants customized their approach to the patient's particular circumstances. Among those family physicians who were comfortable with exceeding recommended doses, olanzapine and quetiapine were the drugs most likely to be prescribed in this way, owing to greater familiarity and clinical experience with these drugs compared with newer agents.

Many family physicians indicated they do not use combination therapy, and refer to a psychiatrist instead if it appears a combination will be required. Among those who were comfortable with combination therapy, the most-often cited drug was quetiapine, for its sedative properties.

7.2.3 Prescribing clozapine

Very few of the family physicians in this study had prescribed clozapine to their patients, preferring to let psychiatrists handle these cases. The one family physician who did have experience with clozapine indicated that approximately 5% of patients were taking the medication. While only a small number of participants had clinical experience with prescribing clozapine, most indicated they would turn to this agent (often by referring the patient to a psychiatrist) only after multiple optimized trials with other atypical agents had failed.

As with the psychiatrists, family physicians pointed to clozapine's effectiveness as the principal advantage, in particular for patients who had not been successfully treated with other atypical agents. Despite their limited experience with clozapine, most participants were familiar with its chief disadvantages: side effects and the need for regular blood tests.

Only two participants felt comfortable answering a question about whether they would exceed the recommended dose of clozapine. Both indicated they would not exceed the recommended dose, owing to the risk of adverse side effects and their limited experience.

7.2.4 Differences when treating adolescents with schizophrenia

Generally speaking, family physicians had less clinical experience with adolescent patients living with schizophrenia, as these were more often referred to a psychiatrist early on. Even those who did opt to treat an adolescent patient sought a second opinion from a psychiatrist.

Those who had treated adolescents with schizophrenia tended to use a more cautious and conservative approach than for adult patients with respect to dose. They started at lower doses, progressed more slowly, and rarely exceeded recommended doses. They also indicated they are generally more wary of side effects in younger patients. In addition, several participants indicated they do not feel comfortable moving to combination therapy with adolescent patients, and most also indicated that they would not initiate clozapine for an adolescent patient.

7.2.5 Assessment of information sources on atypical antipsychotic agents

Respondents to this question largely pointed to continuing medical education (CME), journals, and professional colleagues as their primary source of information when choosing drug therapies for adults and adolescents with schizophrenia.

Most family physicians had moderate to little awareness about available evidence to guide the use of antipsychotic agents at higher-than-recommended doses. Many also called for specific clinical guidelines on exceeding maximum doses and combination therapy. While some general practitioners (GPs) suspected that guidelines on the use of antipsychotic combination therapy exist, none had actually seen or consulted these guidelines. Many were concerned about potential liability stemming from prescribing combination therapy and, as a result, often referred to a psychiatrist to garner specific information on the approach to this prescribing strategy.

While some family physicians had a sense that there is evidence to guide the use of clozapine, none had actually consulted these studies, preferring to leave the prescribing of this drug to psychiatrists.

Family physicians called for more information on many of the key topics covered in the interview, including the range of AAPs available, combination therapy, safety at various doses, and clozapine. CME and online information from trusted sources were the preferred methods for accessing this information. A small number also indicated they valued information on specific agents presented to them by pharmaceutical representatives.

7.2.6 Results of thematic analysis

Analysis of the interviews with family physicians revealed a similar set of themes as with the psychiatrists. The theme of uncertainty surrounding prescribing decisions was even more pronounced among family physicians, as compared with the comments by psychiatrists. In many of their comments, participants used terms like “I guess” and “I think” to preface their position, and the notion of “comfort” with a decision was often observed. A number of family physicians also pointed to the same lack of evidence and guidelines that psychiatrists described. In terms of the tension between decisions based on evidence and those based more on clinical experience, family physicians were more likely to rely on published evidence and guidelines. Very few of the family physicians we spoke with expressed a level of confidence in their clinical experience similar to that expressed by many of the psychiatrists. In fact, they

were more likely to rely on the clinical experience of a psychiatrist. As with psychiatrists, family physicians often looked to others for a second opinion or a higher degree of expertise before making choices on therapy. Indeed, the comments of participants often included referrals to psychiatrists.

As with psychiatrists, a number of family physicians pointed to the unique challenges of collaborating and negotiating with individual patients living with schizophrenia. Compliance was an issue for these care providers as well, although not to the same extent as the psychiatrists with whom we spoke. Perhaps owing to their work in primary care settings, family physicians focused a great deal on the role of the patient's family in the overall care of that patient. Similar to the experience of psychiatrists, families were seen as key allies and, to a lesser extent, part of the challenge of caring for patients living with schizophrenia.

Finally, family physicians often came back to the unique challenge they and their patients face of waiting for a referral to a psychiatrist.

8 STRENGTHS AND LIMITATIONS

The strength of this study lies in the quality and richness of the comments offered by participants. Interview participants were engaged, informed, and willing to share their sentiments, experiences, and opinions with the moderator. The number and depth of discussions with prescribers — both psychiatrists and family physicians — allowed us to achieve saturation on all the key points we set out to address.

Although saturation was achieved, a limitation to this study may be the small number of participants. There may also be an inherent self-selection bias. Participants were invited and remunerated to participate in the study. We also note that not all provinces and territories were represented in our sample. As formularies and public insurance plans can vary from one jurisdiction to another, this may be a limiting factor. Practice patterns may also vary across regions for other reasons.

9 DISCUSSION

This study shed light on what many psychiatrists acknowledge is current practice in their field: the prescribing of higher-than-recommended doses of AAPs and combinations of antipsychotics for patients with schizophrenia who do not have a sufficient response to recommended doses of a single agent. These practices appeared to be based primarily on individual clinical experience and the opinion of leaders in the field. The need for simple, well-tolerated therapy was cited as an important factor in maintaining treatment adherence. Many psychiatrists appeared to favour increasing the dose of antipsychotic monotherapy (including above-recommended doses) as an initial strategy when faced with relapse or suboptimal response, possibly because this was felt to be simpler for the patient than a change in therapy. Combination therapy with agents felt to be complementary to one another was also cited as a treatment strategy. Interestingly, the agent most commonly added to existing therapy was quetiapine, for its sedative properties in the treatment of symptoms such as agitation or restlessness. Ultimately, it appeared that the most important determinant of the treatment strategy for most participants was individualization of therapy to fit the specific circumstances of each patient.

Participants — both psychiatrists and family physicians — acknowledged that evidence and guidelines for both high-dose and combination therapy with AAPs are lacking. In the absence of such evidence, prescribers turned to clinical experience and the individual response of each patient for guidance. It should be noted here that family physicians were far more likely to turn to the clinical experience of psychiatrists than their own experience or that of other family physicians. Indeed, most were reluctant to prescribe multiple agents or higher-than-recommended doses, preferring to let psychiatrists treat patients requiring such strategies. The two professional groups were similar in that there was a degree of discomfort in prescribing high-dose and combination therapies in the absence of sufficient evidence. In the case of psychiatrists, these gaps in evidence did not appear to pose a barrier in implementing these strategies when they were felt to be appropriate for a particular patient.

Many of the prescribers with whom we spoke regarded clozapine highly for its efficacy, although all acknowledged that the requirement for regular blood testing makes this a challenging therapy for many patients living with schizophrenia. Still, the drug is valued as a therapeutic option for patients who fail to achieve satisfactory results with other atypical antipsychotic agents. In general, respondents appeared to favour dose escalation and combinations of non-clozapine alternatives before initiating clozapine, despite acknowledging that there was good evidence for the superior efficacy of clozapine, and poor evidence for high-dose and combination strategies. There were three main perceived barriers to prescribing clozapine: adverse effects — particularly the risk of agranulocytosis, weight gain, and seizures; the administrative burden of initiating and continuing clozapine, and requirement for regular laboratory monitoring; and patient reluctance or non-adherence due to the adverse effect profile (particularly agranulocytosis) of clozapine and requirement for regular blood tests.

Patients with schizophrenia were not included in the present study; therefore, the perceived resistance of patients to clozapine use and the risk of non-adherence could not be confirmed. Nevertheless, the experience of psychiatrists in this regard suggests that there may be an opportunity to educate patients and family members about the risks and benefits of various treatment strategies for schizophrenia, thereby enabling more informed decision-making in collaboration with health care providers.

Most of the family physicians with whom we spoke indicated that they would not initiate clozapine, preferring instead to refer the patient to a psychiatrist. A certain degree of frustration was also expressed regarding the wait times involved in referring to a psychiatrist. This suggests that some patients with poor response or relapse may remain on suboptimal therapy while awaiting referral. Increased capacity on the part of family physicians to manage such patients could therefore result in improved outcomes. Further study would be required to determine the specific barriers family physicians perceive in managing treatment-resistant patients. However, it is possible that continuing education strategies aimed at increasing awareness of evidence-based approaches to treat such patients would be helpful to this group.

The management of adolescent patients with schizophrenia was an area of particular uncertainty for many of the physicians with whom we spoke. None of the participants specialized in child or adolescent psychiatry, so their clinical experience with such patients was limited. All expressed considerable caution when treating this population, preferring to stay with antipsychotic monotherapy within recommended doses as much as possible. Indeed,

even some psychiatrists acknowledged a preference for referring these patients to other psychiatrists more focused on this age group.

The physicians who participated in the study expressed a preference for learning from their peers, either through published, peer-reviewed literature, CME events featuring experienced psychiatrists, or more informal interaction with peers in the community. These avenues of dissemination may be most fruitful for strategies aimed at increasing awareness of evidence related to antipsychotic therapy among psychiatrists and family physicians who treat schizophrenia.

APPENDIX 1: EXPERT COMMITTEE AND CONTRIBUTORS

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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 from Amgen Canada Inc. and Merck Frosst Canada Ltd. to the Alberta Kidney Disease Network.

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 I clinical trial with Neurocrine Biosciences Inc.

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.

APPENDIX 2: MODERATOR'S GUIDE FOR CURRENT PRACTICE INTERVIEWS

1. Introduction

1.1. Before we start, I would like to explain a few things about this study and today's interview.

- The study is being undertaken by the Canadian Agency for Drugs and Technologies in Health (CADTH) — a not-for-profit agency funded by the federal and provincial governments and mandated by them to provide credible, impartial advice and evidence-based information about the effectiveness of drugs and other health technologies.
- This study is focusing on the prescribing of atypical antipsychotics for schizophrenia in adolescents and adults, specifically treatment strategies involving higher than recommended doses or combinations of antipsychotic agents.
- The interview will last 20 to 30 minutes.
- There are no observers listening in on the conversation.
- The interview will be audio-recorded to allow for a more detailed report; audio files will remain the property of the research firm and will be erased after 12 months.
- Your participation in the interview is strictly voluntary and you need not answer any question that makes you feel uncomfortable.
- Your identity will be kept confidential in all aspects of the study and in the final report.

1.2. Are there any questions or concerns related to this study?

2. Drug Therapy for Schizophrenia

I'd like to start by asking you some questions about your opinions and current practice regarding drug therapy for *adults* with schizophrenia.

2.1. Do you often treat patients with newly diagnosed schizophrenia or first episode of psychosis?

<If yes, proceed to 2.2, if no, jump to 2.6>

2.2. What class of antipsychotics do you typically prescribe as **initial treatment** for your adult patients with newly diagnosed schizophrenia: typical or atypical antipsychotics? In your opinion, what are the clinical advantages of this approach?

2.3. What are the main factors you consider as you determine the **optimal dosage** for a particular adult patient?

2.4. Do you ever use **combinations** of antipsychotic agents as **initial** therapy? If so, under what circumstances?

2.5. How do you judge whether initial treatment is **effective**?

2.6. How much time would you give the initial treatment before moving to a new strategy?

2.7. What **doses** would you use before deciding to change treatment: Up to maximum recommended doses or beyond maximum recommended doses?

<Probe for key determinants of highest doses tried; i.e., relative importance of: (a) recommended doses, (b) patient tolerability and (c) response>

2.8. Approximately what fraction of patients with schizophrenia seen in your practice have (or have had) a **suboptimal response or relapse** on recommended doses of multiple antipsychotic agents used as monotherapy?

<Suboptimal response = disease severity bad enough to require change in treatment strategy>

2.9. What is your **preferred approach** for patients who have relapse or suboptimal response on antipsychotic agents used as monotherapy at doses within the recommended range?

<Probe for: (a) trial of another typical or atypical agent, (2) use of higher-than-maximum doses, (c) use of antipsychotic combinations, (d) use of clozapine>

<If more than one strategy is commonly used, probe determinants for choosing one over the other>

2.10. *<If high doses are indicated as an option>* Are there certain drugs for which you are more likely to use higher-than-recommended doses, and if so, why?

2.11. *<If combination therapy is indicated as an option>* Are there certain combinations of antipsychotics you are more likely to use than others, and if so, why?

2.12. Under what circumstances, if any, would you consider using higher than recommended doses of an antipsychotic, or combinations of antipsychotics? Do you prefer one strategy over the other?

<Probe determinants for using each of these two strategies>

2.13. Do you ever prescribe **clozapine** to your patients with schizophrenia? Approximately what percentage of patients with schizophrenia are treated with clozapine in your practice? *<If never prescribes clozapine, jump to question 3.1; otherwise, proceed>*

2.14. Under **what circumstances** would you consider using clozapine for an adult with schizophrenia?

<Probe for the stage at which clozapine would be considered; i.e., how many other antipsychotics would be tried, whether combinations and high doses would be tried before going to clozapine>

2.15. In your experience, what are the main **advantages and disadvantages** of using clozapine?

<Probe for perceived risk or frequency of agranulocytosis or neutropenia (an adverse effect of clozapine in which white blood cells are adversely affected)>

2.16. When you prescribe clozapine, would you ever use **higher-than-recommended doses**, **or combinations** with other antipsychotic agents? If so, under what circumstances?

Now, I'd like to ask you the same questions but relative to your treatment of *adolescents* with schizophrenia.

2.17. *<Same line of questioning as in adults, beginning with screener to determine if adolescent patients are treated by the respondent to any significant degree>*

3. Information Sources

3.1. What would you say are the primary sources of information you use to guide your choice of drug therapies for adults and adolescents with schizophrenia?

<Probe for: Information from pharmaceutical companies>

<Probe for: Clinical Guidelines — which in particular?>

<Probe for: Journals>

<Probe for: Opinion leaders>

3.2. What are your thoughts regarding the available evidence to guide the use of antipsychotic agents at higher-than-recommended doses?

3.3. What are your thoughts regarding the available evidence to guide the use of antipsychotic combination therapy?

3.4. What are your thoughts regarding the available evidence to guide the use of clozapine?

3.5. Are there any issues, uncertainties, or controversies you would like to see more information on? If yes, please explain.

3.6. What is your preferred method of receiving information on drug therapy for patients with schizophrenia?

<Probe for: Written materials, conferences/workshops, lectures, journal articles>

4. Conclusion

4.1. Do you have any final thoughts or comments on high-dose or combination antipsychotic therapy for patients with schizophrenia?

Thanks very much for your participation today. I appreciate your time and your thoughts. An incentive cheque will be sent to you within a few days.

APPENDIX 3: QUOTES FROM PSYCHIATRISTS

Initial Treatment

Atypical. The first advantage is that I mean I would not face the old side effects of the typical antipsychotics. I mean bradykinesia, tardive dyskinesia, extrapyramidal side effects, tremors. And at least the patient will have a better quality of life. — ***Quebec***

Atypical. Well, I think you have a different set of side effects with atypical antipsychotics, so it's not really their efficacy per se, it's their lack of traditional side effects, lack of tardive dyskinesia and movement disorders — well, not lack of — decreased incidents of tardive dyskinesia and movement problems. — ***British Columbia***

Atypical. The advantages are that the atypical antipsychotics are better at preventing relapse and they have a more broad spectrum of activity. They don't just treat positive psychotic symptoms. To some degree, they cause fewer negative symptoms and may improve some negative symptoms and cognition, and in particular there's evidence that they facilitate neurogenesis and prevent the loss of cerebral cortex that can happen with schizophrenia and the use of typical antipsychotics over time.
— ***British Columbia***

Atypical. I'm very familiar with the data and with the lot of the debate that looks at typicals and atypicals, and it looks like, in terms of efficacy, there isn't that much of a difference. I don't really believe that clinically. I think overall there are certain domains where the atypicals have better efficacy... Negative symptoms in the mood symptoms, in some of the cognitive symptoms. And if you look at what affects functionality, it is much more those symptoms particularly, some of them cognitive symptoms. And I think that the atypicals do have an advantage in that area. I think some of the side effect profile is also better, not that it's perfect because there's lots of problems with the atypicals as well. But particularly in the movement disorders and tardive dyskinesia, which is a horrible side effect, often permanent, is very rare with the atypicals. In terms of cleaning the hallucinations and the delusions, they both do them very well. — ***Ontario***

Second generation. I don't think there actually are any clinical advantages. It sort of seems like it's standard of care. It's like what your peers are doing, what your colleagues are doing, so you just kind of tend to go along with that. Like I'm familiar with the CATIE study. I don't have a problem with the first-generation antipsychotics. I'd like to use them more, but it just seems that that's what your peers are doing, so you just tend to kind of follow that a little bit. — ***British Columbia***

Determining Optimal Dosage

Well, I usually start off within the recommended dosage range for that particular patient. And based on my clinical observation, I might make a decision to increase the dosage within that range, and to try and optimize the trial as much as possible, so optimization meaning that there's enough medication for a sufficient duration for it to bring remission. If after a certain amount of time I don't see any sort of positive movement, then I might consider pushing the dosages or using other strategies. — ***Quebec***

Well, it's usually a balance between efficacy and tolerability. In newly diagnosed patients, one often starts at a very low dose and then titrates up because sometimes the doses necessary or maybe half as much as somebody with chronic schizophrenia. I'll try to figure out with the patient what kind of side effects they might not like the most or what they might tolerate, and sometimes one uses the side effect profile to work in your favour. For instance, if sedation is a welcomed side effect because of sleep problems, one might choose a medicine that's somewhat more sedating. I also try to pick medicines that are generally going to not cause as many complications in the long run, such as metabolic syndrome as first-line medicines and only if required go to medicines that we know are more likely to cause metabolic syndrome if, because there's a lack of response. — ***British Columbia***

*Well, sometimes it makes a difference if they're male or female. It makes a difference if they have medical illnesses. It makes a difference just how severe their symptoms may be, what the symptoms are. If the person's more agitated or they're just not doing anything. It depends on the symptoms, largely, and past history. — **Quebec***

*It depends on the clinical presentation and also the age of the patient, obviously. These are the factors I think are important, and based on that, we'll decide what the dosage is. — **New Brunswick***

*So in terms of the gender, I might go lower with the female, and also in terms of racial as well; if they are South Asian, then I might go lower dosing on that. Well, generally, at least in my training, the females and South Asians or Southeast Asians are a bit more sensitive because they don't metabolize the neuroleptics as rapidly, so therefore they don't need as much because their blood levels are… they don't use much because the body doesn't metabolize as quickly the medications. So there's a number of factors that I look at. It probably really comes down to the severity of the psychosis, the level of agitation they're having. I mean, really, if this person's calm, then I might start at a much lower dose. If they're very agitated or aggressive and in restraints, then we might actually start off with a very, very high dose. But I mean the gender and race do have some — when I look at the dose and I sometimes think about that. — **Ontario***

*There are few factors I consider. Number one is the weight of the patient — how big is he? I look at the gender. Usually females don't tolerate as much as the males. Sometimes the race of the patient. For instance, the Asians, they don't take as much as the Caucasians. I look at the severity of the illness. If somebody is really psychotic, sometimes I have to go much above the recommended dosage of the medication in the CPC... Yes, so the clinical response. So sometimes what we are told to do may not work with everybody, that we may have to increase the dosage. — **Alberta***

*If I'm facing an old patient, I will start low and raise low, gradually low, and slowly. If it's a regular adult, no, I will start the recommended dosage in the literature... There is sub-cultural differences sometimes. Several years ago, when we were using the typical antipsychotics, we had to watch with specifically African-American culture that are more sensitive, too, but I'm talking regarding typical antipsychotics, not atypical. — **Quebec***

*Clinically, like you want to get symptom control versus side effects, right. So sometimes you do go a bit over the recommended doses. I tend to not with risperidone because to me, risperidone's more like a typical antipsychotic, so it's great, but I don't usually go over 6 with risperidone in my clients. But olanzapine I have gone to 30 with. You look at the manufacturer's recommended dosage sort of as a guide. But there's some people who are fast metabolizers, clearly... Or if they smoke, like that burns through olanzapine, so sometimes people need higher doses. — **British Columbia***

*In terms of the dosage? Well, typically I do look at what the recommended doses are. However, you have to look at the individual patient. The majority of the medications of the atypical antipsychotics are metabolized at the level. There, in fact, it's only one oral one that is not, and that is Invega or paliperidone. So there are individuals that can be rapid metabolizers, that can be slow metabolizers where you will have a variation in terms of dose, where you would need sometimes if you're an extremely rapid metabolizer or a rapid metabolizer, you may need a higher does than what may be recommended. — **Ontario***

*There are some drugs where, for example, olanzapine and clozapine, if the patient smokes, their metabolism will clear the drug at a higher rate, so you need to give them a higher dosage of the drug. Other drugs aren't affected by smoking — say, for example, ziprasidone. So you can ease up a bit on the amount you give the person. — **British Columbia***

There is also the issue of polypharmacy. Many patients are not just on one atypical; they're often on two, but they're also on other medications, antidepressants, mood stabilizers, you know, medications, other reasons as well. So that can affect the actual doses. Sometimes you have to exceed the

*recommended dosages... Also, the patients that are used in the clinical trials are your perfect patients, really, that don't have other disorders, they don't abuse substances. Real-life patients are a little bit different. So those doses are not really based on real-life patients. — **Ontario***

*I take into account a number of factors. One, obviously the severity of the psychosis; the presence of any comorbidities; three, existing or previous treatments; and four, probably initial tolerability and response, so I will start at a small dose and then titrate that up accordingly to both clinical response and also side effect profile. — **Alberta***

*Well, if it's a first episode, that'll affect the dosage versus whether they've had previous illness, how long they've had a previous illness, how severe the previous episodes have been. Yes, I think I would start with that. So the severity of the current illness, the severity of previous illness, and the chronicity; how long it's been, and the previous medications that they've been on. — **Quebec***

*Yes, the variables. Then of course the family or financial variables. For instance, the new drugs are extremely expensive, but the older drugs are cheaper. Although the older drugs may have more side effects, like what they call tardive dyskinesia, or TD. So most of the psychiatrists prefer the newer ones. Then the problem is about the newer ones may not be under the Alberta Government plan. — **Alberta***

Combination — Initial Therapy

*Not as initial therapy. Well, it's more a question of disadvantage. The disadvantage of combination would be a higher incidence of side effects. There's no reason to start with that when there's a fair chance that we'll get a response with a single agent. — **Ontario***

*It's also I kind of have the "Keep It Simple" principle where one medicine — because adherence is such a huge problem, especially in schizophrenia — keeping the treatment simple, one pill once a day if possible, people are more likely to adhere to that. — **British Columbia***

*Rarely, but occasionally I might do it if I'm giving something that I think may not be very sedating and I think they also need something sedating, particularly at nighttime, I might add a different one for sedation for nighttime, yes. But not usually. — **Quebec***

Assessment of Effectiveness of Initial Treatment

*I would judge that by going through the symptoms with the patient on interview and see how the medication's affected the symptoms. — **British Columbia***

*Usually by seeing whether there's any signs of early response, and by early response the definition is usually a 20% decrease in symptoms within the first two weeks. So there's got to be some evidence of some response within those first two weeks, otherwise it's unlikely that they're going to respond. That tends to be a predicator of response, of later response, and a fuller response. So we usually go by that. — **Quebec***

*If it's psychotic symptoms specifically that I'm targeting, then I'm looking for reduction of those particular psychotic symptoms. These drugs are also used for other target symptoms besides psychosis, so it depends on the target symptoms. But whatever the target symptoms are, we're looking for a reduction, if not elimination of those symptoms. — **Ontario***

*Obviously the clinical presentations, so if the patient is showing improvement, the symptoms will be the best for judging the improvement. So psychosis, like hearing voices, visions, thought disorders, mood instability, and then functioning level, and how much they're able to interact with people, and how much more functional they become. — **New Brunswick***

*So then really it's the positive symptoms and functioning. So I don't really think that they help the negative symptoms of schizophrenia that much. So, unfortunately, I wish they did, but if their positive symptoms are either gone or they're on a level that they're not interfering with their functioning, like they might have some residual psychosis, but they can kind of sort of ignore it or they have strategies to deal with it, and they're managing to have good functioning. That's kind of what I go for... if they're calmer, and in terms of their level of psychosis, if they start becoming less psychotic and start to have some insight or become less paranoid and have less hallucinations, then I think it's starting to be effective. — **Ontario***

*Well, it depends on the timeline. I mean, in the first couple of weeks I hope to see an improvement in anxiety and in sleep, and in the person's ability to establish a rapport with me, and be more trusting. So I'd like to see that as an initial response within a couple of weeks. But in order to see a significant decrease in the psychotic symptoms, I'd like to see that in about six weeks. — **Ontario***

*Again, it really depends on the adequacy of the trial, so that's taking it to the dose that I would see as an effective dose, and continuing that for a reasonable period of time. That in itself is kind of predicted to a certain extent by the patient's response or lack of response. So if a patient starts to respond with some reduction in psychotic symptoms, and the drug is well tolerated, then I would continue probably with that medication, and increase the dose accordingly. If there was no response at all, then I probably wouldn't pursue it for any length of time. I would switch fairly quickly to something else. — **Alberta***

Timing of Initial Treatment

*I'm usually seeing my patients, at most, a week later, usually sooner after I start a medicine; at least, I'm hearing from them sooner. And I'm looking for a significant response within a couple of weeks or something has to be changed if you're not getting that, because these medicines, contrary to some earlier sentiment, do work quickly. And I'm looking for a signal of are people starting to improve within two weeks. — **British Columbia***

*And the duration of treatment, in my opinion, should be at least four weeks, because that's the minimum amount of time to start achieving a significant improvement in the psychotic manifestations, such as auditory hallucinations and delusional ideation. — **Quebec***

*At least six weeks' trial. I try to go up to eight weeks, if I can. If the patient is not decompensating, then I would try for eight weeks for the optimum effect. — **New Brunswick***

*So, going forward, yes, I think it's different for everybody. I think that, and again, I don't do a lot of hospital in-patient work, but if an antipsychotic is fully ineffective, it takes me probably — unless there's dire symptoms where they really need to be hospitalized. In the outpatient setting, usually I would increase the dose, you know, every visit, and that might be every week or two. So I don't know, perhaps six to eight weeks. That's just a ballpark, though, and it would really vary individually. I may go on a lot longer if the patient has very mild symptoms and we're really trying to increase or push the dose or it might be shorter if the patient's very ill. — **British Columbia***

*It depends on the clinical situation. If somebody is beating at the staff or even the physician, you know, you may have to increase the dosage. So usually, it depends if the patient is in the in-patient set-up or outpatient set-up. It depends on the severity of the illness, and the symptomatology, and, to some extent, the acceptance of the medication by the patient. — **Alberta***

Well, assuming it's well-tolerated, reasonably tolerated, and that there are no intolerable side effects forcing discontinuation sooner, if it's just efficacy, effectiveness that I'm looking at, then it depends. I'm looking for at least a hint of improvement in the first couple of weeks, let's say two weeks. And at about four to six weeks, I'm figuring we've got most of the improvement at that point. But there certainly can be further improvements over the next few months, but if I've seen nothing at all by way of improvement in four to six weeks, absolutely nothing, I'd be starting to think about switching. And if

*it was a more severe acute state, I might not give it as long as that. It might be quite a lot quicker if the person's at a highly agitated, very unstable state. It'd just be days. — **Ontario***

*Okay. Depends on my way of practising: if I'm practising in the hospital for in-patient or I'm practicing in an outpatient clinic...In hospital I will raise the medication every week. If I don't see any improvement at all, I will raise it. If I see some improvement, I will raise it slower. I will try to optimize my dosage to the maximum effective and recommended dosage of each medication. As an outpatient, usually they are less sick in comparison to the patients who are hospitalized. So I can raise the medication and start the medication and see them after four weeks. And I'll see if there is an improvement or not. — **Quebec***

Dosing Decisions (Up To and Beyond Maximum Recommended Dose)

*I would certainly consider going beyond. Again, I would tend to look at why there isn't a response at the maximal dose. So is it a compliance issue? Is it a drug-drug interaction issue? If I'm satisfied that there's no other confounding factors, but the patient is still responding to the medication, but hasn't quite got to where I want him or her to be, then I would still continue increasing it past the maximum recommended dose. — **Alberta***

*I tend not to go beyond maximum doses, but I may not even go to the maximum dosage. It depends on the patient's profile and age. If somebody is quite young, say… the early 20s, we are talking about adults, not adolescents, right? So early 20s and maybe 19, 20 years old, and they are medication naïve, never had any medication, never used any drugs or alcohol. So their system is fully naïve. In that case I may not even go up to the maximum dose because these patients tend to get side effects early on, even at that lower dose. Usually the lower doses also become effective for these people. Well, in terms of changing the treatment,then in that case I would go up to the maximum dose unless the patient is having any intolerable adverse effects. If they don't, then I would go to maximum dose before changing. — **New Brunswick***

*I wouldn't exceed the recommended dose, no. I don't know, maybe I should, maybe I should be getting levels, but generally if I'm not seeing some improvement at say like 50% of the dose, the maximum dose, then I'm thinking this isn't working. Would I push it? I just want to see something. By the time they're like 50, there's three-quarters of the maximum recommended doses, I want to see some improvement. If there's no improvement at all, then, yes, I'm starting to think I'm not on the right track, so I might switch, yes. — **British Columbia***

*That depends. If they're having a lot of side effects and I haven't been able to optimize and maximize my dose because of some of the side effects, then I may add another medication. If it's a question of that they are tolerating the side effects, but there's just not… haven't had a resolution of their symptoms, then I will increase the dose. And if they're still tolerating it and they're still not sort of what I would call in remission, then I might exceed those doses in those patients. — **Ontario***

*If it's well tolerated, yes, the answer's yes. Yes. No, up to the recommended dose. Or it depends. I might go slightly above the recommended dose if it's well-tolerated... I use the term "tolerability" deliberately because if the patient tells me and if it's pretty clear that their side effects are intolerable, then I won't continue with the medication. And if they're in any way dangerous side effects. But there's a lot of subjectivity involved as to how bothersome a side effect may be, but it's also obviously got to do with how much it's really affecting the person's functioning objectively. — **Ontario***

*I would go to maximum recommended doses. For some medications, I could go beyond. There's certain atypicals for which I don't go beyond. For Risperdal, I'm not going to go beyond 6 mg because I know it's going to cause too much EPS. For Zyprexa, the recommended dose, I don't know if it's 20 or 30, but I have put patients on 40 because there isn't as much of an issue with akathisia and extrapyramidal symptoms. So, depending on the molecule. The side effect profile of that molecule. — **Quebec***

Patients Experience Suboptimal Response on Recommended Dose

*Maybe about 10%, if you're talking about trying many different ones, maybe about 10%. Fifteen per cent, maybe. — **Quebec***

*What percent with multiple? Maybe 20%. — **Ontario***

*I consider if the response isn't really as good as I'd like, but I don't really believe the change in medicine is going to make a difference. So that being the case, I'm going to lower the suboptimal response from 75% down to 30%. — **Ontario***

*Sixty per cent, maybe. And suboptimal is an odd definition, but certainly in terms of either having the quality of life impaired by symptoms or continued symptoms despite optimal treatment. Yes, I'd say at least 60... a lot of people continue to have symptoms, but it doesn't impact their quality of life very much. So in that case probably 30, maybe 30%. — **British Columbia***

*I think I can answer it. Because I'm seeing first episode people, even though they've been sometimes had a long duration of untreated psychosis, most of my patients respond optimally, actually. You can get people well early in the course of this illness, which is the rationale for early psychosis clinics. So it's a small percentage. I'm struggling with one or two people out of 30, so that might be 6% that I have a suboptimal — give me a little time and I can get most people pretty well because they are early in the course of their illness. Not all of them have schizophrenia. Some of them have mixed types of psychoses that may not qualify for a diagnosis of schizophrenia, the drug-induced bipolar disorder associated with psychosis or other types of psychoses. — **British Columbia***

*I'm going to be a little bit specific about this one because what I'm going to mention now is we assume that our patients are taking their medication. So we assume that they are taking the doses that we are prescribing. And we overestimate that and the patients overestimate that. So many times they aren't taking the dose that they're supposed to. So there's an issue with that one, always sort of sceptical about that to begin with. Having said that, there definitely are those that are taking it and they are taking it the way they're supposed to be taking it. And I would say in the early years of illness, and if we talk about the first two to five years of psychosis, I would say that even at therapeutic, maximum therapeutic dose of probably 20% to 30% of patients have either relapse [inaudible]. — **Ontario***

*I'd say 50%. I mean severity of the disease, comorbidities, if the patient is taking his medication, is he adhering to the medication regiment or not? There is lots of comorbidities like substance abuse, like alcohol abuse, like medication discontinuation, like any other comorbidities like a patient who has a lot of physical sickness, like diabetes, hypertension, complexity disorder, like neurological disorder, convulsion, seizure, et cetera. — **Quebec***

*Probably 60% at least. Well, we're talking a new onset illness or are we talking more chronicity, because that's really one of the distinguishing features, I guess. In the new illness, drug selection is not guaranteed. You pick one or another, and the person may have a disappointing response. But if you're fortunate and you've chosen that fairly well-respected drug, so to speak, an effective drug, then the person has a reasonably good chance of responding in the early stages of their illness that they continue to take the treatment... usually because they've been ill for a long period of time, they've probably been non-compliant or non-adherent to their treatment multiple times, had several hospitalizations, relapses. So essentially their illness has progressed, in some cases at least, to a very-difficult-to-treat illness. — **British Columbia***

Approach to Patient Suboptimal Response

Well, monotherapy, that's what we're having, so I have to look in at doses, how much they're taking, are they compliant with the medication? Any other contributing factors into it? Psychosocial stress, drug abuse, and so forth, medical conditions. And if you rule out that there's not another contributing factor,

and the doses of medication isn't enough, then we either adjust the dose or add on, if need be. ***— New Brunswick***

Well, my first choice would be to go beyond the recommended range. I do sometimes use combination therapy, even though there isn't really a good rationale for it. But I will sometimes do it for various reasons. One, I might add a second one that's more sedating to help with sleep at night. So that's one reason why I may use that one. Or there may be a medication that is used and it's not sufficiently effective, and a higher dose won't be tolerated, but I'm hoping that a second medication will be tolerated. So it might be that I'm hoping, even though the side effects of the two together could conceivably be worse, I'm hoping that the total side effects will be more tolerable with the two as in a higher dose of one. — ***Ontario***

Because if they've been doing well for a long period of time on this medication, I would probably try upping it, say if they were at a low dose. There are so many variables here. Did you say already at the max dose? So if they're at the max dose but they've been on a long time they'd be doing well, might do a level. And I might think about upping it above the maximum recommended dose. But if they've only been on for a short period of time, then I would probably switch it or add another one. ***— British Columbia***

Again, it sort of depends on the patient, but there are a few different possibilities. One is not combining the medications. And sometimes you might boost the medication — well, sometimes you might just combine two antipsychotics, sometimes you might combine an antipsychotic with some other medication. Sometimes I don't know what to do and I'll ask for a consultation with a colleague. My preferred approach would be clozapine. Well, for those people did it work for, terrific. Of course it doesn't work for everyone, and not only does it not work for everyone, but then some people have to stop because of the harmful side effects they can get with it. But when it works, it's, like, magnificent. So you have a chance of getting something… and of course that's what you have to do when you put someone on clozapine, they have to have trials with a few other medications first. There's your opportunity to do that, and possibly a medication that could work. There's no guarantee with it, and even if it works there's no guarantee that someone's going to stay on it. — ***Quebec***

First of all, you have to do an assessment and figure out why they relapsed, and the most common cause is non-adherence. And if it is non-adherence, usually you can arrive at that. You want to understand why they have had non-adherence. Is it because of a lack of efficacy or is it because of a lack of tolerability? Is it both? Is it because of their illness? Is it because they're in denial? Is it because they tried to go off meds, didn't want to share that? So you have to do a thorough assessment as to why there was a relapse. A suboptimal response — somebody who you just can't get well — same thing. You want to see are they taking their meds? So then my response will be depending on what I think the problem is. If it's truly that they haven't responded to one or two atypical antipsychotics, then I'll go to clozapine because I know it works better. Sometimes if they won't accept clozapine because of the blood work, I'll go to olanzapine because it's clozapine-like. So that's usually my strategy is to try to determine why, and then adjust accordingly. I must say I loathe polypharmacy. Usually I'm sticking to one atypical drug. That doesn't mean that I've never had someone on a combination. I play with a crossover, a switch, but sometimes people are really sick, they're not getting well, they're on a maximum dose of clozapine. You try adding a little bit of risperidone, they get better, great. — ***British Columbia***

Well, here's the thinking, and I think this has clinically been proven time and time again. If you study relapse data, so in other words, who gets back to the hospital and how frequently, as soon as you introduce an injectable antipsychotic that is well-tolerated, and that's the operative phrase, of course, you're at least guaranteeing that degree of adherence because 75% of schizophrenics are non-adherent to their pills. Therefore, they rarely take their pills. So when you inject antipsychotics, either as monotherapy or in combo therapy, you know that they're getting the injectable med. Now, in the adherent patient, you may add a certain element of treatment advantage by having them on an atypical plus an injectable because the injectable is sort of a guarantee minimum, how much they're going to get a drug on a daily basis. And then if they continue to take the oral agent, they may get an antidepressant

*effect, plus it may just make the injectable work a little better because you're covering more bases in terms of the treatment approach. That's sort of the logic that's out there in 2010. — **British Columbia***

*So there are different circumstances for each, so I can't say whether... it's not a blanket statement that I'd prefer one over the other because there are some medications that I won't use at higher-than-recommended doses. Risperdal, because we get into too much EPS and akathisia. So if there's Risperdal on board first, with Risperdal I would go the combination route, not the higher-than-recommended dose. With Zyprexa, if I'm not having enough effectiveness in a response, then I can go the higher-than-recommended dose route. So it depends on the medication, basically. I don't have one preferred. It depends on which medication it is that's on board first. — **Quebec***

Clozapine Prescribing

*Well, I have a few times, but I'm in an acute care hospital, and so we have acute care units, so I've started a few times. When I worked at [Name of Facility], which is a chronic care facility, I've started a lot more times in that facility. But yes, I've started clozapine before, I've switched people to it. Probably not very many [of my current patients]. Maybe 3%, 5%. — **Ontario***

*Absolutely. I have from the day it became available in Canada. I would say less than 10%. And I should also say that I'm probably underutilizing the drug. It is a very effective drug. — **Ontario***

*I would say probably these days getting up for… How many patients do I have? I'm thinking, to give you an accurate answer, I have 90 patients at the team is probably I have at least eight people on clozapine. I'd probably say of my patients with schizophrenia at least 10% to 15%. — **British Columbia***

*Yes, I prescribe it, and I would say about 25%. — **Quebec***

*I wouldn't. I would send a patient to someone who is more specialized if I was going to do that. — **Quebec***

*Clozapine is supposed to be the king of the antipsychotics, and usually it gives a very good response. But I am very, very cautious not to put people on clozapine because of two or three reasons. Number one, the weight gain: it is a big problem. Number two, the cost for the health care is a big problem. I think about $10,000 per year. Number three, I'm concerned about the inconvenience of the patient having to check the blood in the beginning, about every two weeks, then at least once a month. So I have about 16 patients on clozapine, but I don't use it as a first line. — **Alberta***

*Basically when you don't get a good response from the other medications, either because of side effects, they can't tolerate the side effects, or they're treatment refractory to the other medications. The standard of care is that once someone has been treatment refractory with optimal trials of at least a couple of the medications, then they're candidates for clozapine, and it's a good medication, right? There's good evidence for it, and people do well on it. So it's sort of standard of care, I think. — **British Columbia***

*Two. I'd say after two failures, considering clozapine. Definitely. Not after one. Sometimes they won't want it and they'll try something else. Certainly after two failures if I've been able to prescribe, without being limited by side effects. If it's efficacy then I'm certainly going to think of clozapine. — **British Columbia***

*So usually for patients who are more, either refractory — so that have failed three atypical antipsychotic combinations — or patients who are having too much EPS with any of the atypicals or patients who have TD — tardive dyskinesia — clozapine will help with that as well. — **Quebec***

If he's refractory to other atypical antipsychotics, not responding. If he's a patient who refused treatment and I'm obliged to take a court order to force him to get his treatment. And I want to make

*sure that he's receiving his injection. At least he has the medication in his blood for the next month. I will go with clozapine. And typically with a general person — I know you touched on this, but I just want to reaffirm — you would likely use clozapine after many of the monotherapies have been tried and different combinations of some of the other atypicals, and then you would clozapine as a last resort. — **Quebec***

*Well, certainly if someone who is defined as treatment resistant where you've tried a number of the different antipsychotics, and they've had appropriate dosages, and still have continued to be symptomatic. They've relapsed or they haven't been able to tolerate them, I then go to clozapine. In someone where there's a very high suicide risk and they're psychotic, clozapine is the only atypical that has proven anti-suicidal properties in the United States. In fact, it has as one of the indications in anybody who's schizophrenic. So that, that's a big advantage. And I often will go to it. I mean, I certainly don't go to clozapine after you've had one failure, but I do if you've had two failures with atypicals. I'll go to clozapine. — **Ontario***

*The only antipsychotic that's ever been reliably, statistically demonstrated to be superior to the rest. The others are pretty much equal with only subtle differences. There's none that get separated from the rest of the pack, except for clozapine. And it's specifically shown to be effective in treatment refractory cases. Now, mind you, it's perhaps a modest superiority, but it's a definite superiority, yes, that being the main thing. — **Ontario***

*The main advantages are it's the one antipsychotic that works definitely better than anything else. The second advantage is it has anti-suicide properties. Another advantage is there's less substance abuse when people are on it. It seems to inhibit the need to use abuse substances. Oh, I should mention I believe that it also helps cognition, perhaps. It stimulates neurogenesis, and a lot of people do well, not just for — when I say psychosis, I don't just mean positive symptoms; it helps negative symptoms maybe better than anything else as well. — **British Columbia***

*The main advantage of using clozapine, as I told you, I will be sure that the patient is getting his medication because I can do a blood level. I will be sure that the patient is not throwing away his pills, but at least he's getting the injection. So this is one main advantage. Second of the advantage that I will have with clozapine is the population responders are very high when we are talking about a patient who has been not responding on other atypical antipsychotics. — **Quebec***

*It's got agranulocytosis. You have to have regular blood work. Some people aren't stable enough to do regular blood work. Some people already have a baseline low white count, so you can't get the companies to release the medication to you. Seizures. — **British Columbia***

*The disadvantages are, wow, it's the weekly blood monitoring, there's the agranulocytosis, there's seizures. But the biggest stumbling block has really been the weekly blood monitoring. I mean, it's hard to get patients on it because you worry they will not be compliant with the weekly blood monitoring. So that's been the biggest obstacle, often. — **Ontario***

*The disadvantages are that the medication that has the highest side effect profile in terms of weight gain, metabolic syndrome, all of those side effects can be problematic. Patients don't want to be on medication for a very long period of time. And that's a problem. There's also some cardiac problems, cardiomyopathy. And patients need to have blood monitoring that's done regularly. I'm not particularly worried about the risk of agranulocytosis. I know that it's been reported. I can tell you that in my more than 25 years of being a psychiatrist, I have never seen a patient with agranulocytosis. I have certainly seen patients where their white blood count has dropped and where they get a yellow sticker from Novartis which requires close monitoring of these patients. They just get a weekly blood test, and usually it goes back to normal and it's often because they've had a viral infection or who knows what it is. But I haven't had a huge problem with that. But you do need to do regular blood testing, once a week at the beginning and then every two weeks, and it's now very nice that you can do it once a month. And for the longest time it was every two weeks, and that was a deterrent for some patients. — **Ontario***

*Well, I see more disadvantages in terms of the compliance. As you know, the blood work is a big one and the side effects on the medication, especially the blood dysphasia, weight gain, and the sedation, and all those things. But when it has helped, it really helped tremendously. When it did work, it did work very well. So it's very difficult to compare the advantages and disadvantages, given the fact that side effects are there, and some of the patients become noncompliant because of the frequent blood monitoring which some of the clients really do well. They would do anything to continue with this medication. — **New Brunswick***

*I wouldn't go higher, no. I have used risperidone with it. And it was rather helpful, I would say. What I've seen in my practice, the risperidone seems to be more helpful for those who have severe psychotic episodes and seizures as opposed to olanzapine or quetiapine. So combining these two, I think, is much more aggressive in terms of treatment, and also helpful. So I think the psychotic episodes show significant improvement with combination of these two. — **New Brunswick***

*So, combinations, yes. Higher doses, no. We have stopped doing that several years ago because we had some problems with the anticholinergic side effects with clozapine where we've had patients with abdominal obstruction, severe constipation leading to abdominal obstruction, and we even had a death from clozapine doses towards 700, 800. So now we cap it; we stop at 400 to 500. So we do not anymore use — in my setting, in my hospital, university setting — we do not use higher-than-therapeutic clozapine doses. So for inadequate efficacy, so inadequate symptom control. I've combined it with IM neuroleptics. I've combined it with other atypicals. I've combined it with mood stabilizers, like valproic acid, for example. — **Quebec***

*What happens is, for example, some people smoke, as I've said earlier, and they lose half their clozapine just by virtue of being a smoker. So even if their recommended dosage says don't exceed 300 mg, their blood test might be saying the smoking is just taking away substantial amounts of the drug. So the 300 means nothing. What I do is I look at the serum level of the drug, which we monitor, and it will tell me you're going to have to push the dosage to get to a reasonable serum level, which will then offer them good clinical results. If you under-treat them, then nothing happens. You might as well just flush the money down the toilet. — **British Columbia***

Prescribing for Adolescents

*Actually, with adolescents I'm more likely to try...the metabolic side effects of the atypicals are a big concern, and the younger the patient, the more weight they seem to put on with the meds. So I probably would do atypicals, but just because it seems to be sort of the unspoken standard of care. I'd tend to go probably more to risperidone or I'll avoid it because it's causing weight gain in younger ones as well. And lipids abnormalities, yes. — **British Columbia***

*I think that all around, I would be much more conservative with the adolescents, much more conservative in terms of going to higher doses, in terms of combinations. We know that adolescents react differently. So I think that I would be less aggressive in terms of dosage and dosage increase, as well as combinations. So I would be much more conservative. And maybe that's borne out of the fact that I don't have enough experience, I don't have enough of a comfort level. Whereas with adults I can do more, I'm more comfortable with pushing the limits, the boundaries of dosages and combinations and whatnot. — **Quebec***

*Again, similar to what I would look at in the early psychosis or young adults. So it is primarily determined by clinical response and tolerability, perhaps being a little bit more sensitive to the tolerability issues in children, adolescents, certainly things like cognition and sedation because they would be affecting schooling and I'd also be concerned about metabolic effects because adolescents tend to be that much more sensitive to weight gain and other things like that. — **Alberta***

In general, I know that adolescents are more prone to the metabolic syndrome, and you have to really factor in the adverse effects of these medicines on them. They're not going to be adherent if they're

gaining weight. So we are now actually doing a full metabolic testing on people and counselling before they even see me now, they're going to be getting that. We're very proactive with looking at metabolic syndrome. But I think the main thing with adolescents is to make sure you're treating psychosis. You don't want to be using antipsychotics for nothing, and I think there's a lot of criticism now being levelled at psychiatrists because they're treating — and I don't treat children, but my sympathy goes to my child psychiatry colleagues — difficult children and difficult families. — ***British Columbia***

Adolescents may be a little easier to treat if we're lucky because they haven't been sick multiple times. So I could get away with a lower dosage. The other factor is sort of a realization that careful treatment of a novice, so to speak, to the illness that's required because you don't want to turn them off the treatment, so you have to kind of balance getting them accustomed to meds, not overdoing it with their meds so that they will accept treatment in the future, so they don't say that was terrible, I don't want to go through that again. — ***British Columbia***

You tend to use more combination with adolescents, and I'm not sure if that's because they are sicker. The earlier you get your illness, the more sort of… it's considered to be more of a sign that it's a more serious illness, right? Like, if you get a mental illness in your teens, it's probably more genetic. It's usually a more serious form of the illness. So usually they tend to need more antipsychotics. — ***British Columbia***

Timing of Initial Treatment (Adolescents)

Before deciding to change treatment? Six to eight weeks. Because of the metabolic effect of the liver function. — ***Quebec***

Well, the thing is you'd be going much more slowly with the adolescent. And as I say they were getting worse, you'd be going so much more slowly, it could be weeks and weeks before you consider that that's not working. — ***Quebec***

Again, I think it's probably similar to adults. It all depends on how they respond to the medication, whether there is reduction in symptomatology. If that occurs, then that suggests that the drug is kind of doing what it needs to do, so I would be continuing with that. If there's no response whatsoever, then I would be switching that much more quickly. — ***Alberta***

Dosing (Adolescents)

Probably less likely to go above maximum. I don't know, just because they're younger, I guess. I'm not sure. It's more I'm like just more medical-legal cautious rather than it being because of side effects or anything. I just feel like you got to be more medical-legally cautious with someone who's younger. — ***British Columbia***

It really would depend on the response of the patient. The management of the dosage or the adjustment of the dosage of the medication, the process is essentially the same as with adults, except for the fact that it's a little slower, it unfolds a little more slowly. So I will give the patient a longer period of time to adapt to a dosage I have put them on. I start slow, and I start low and I go slow. So for example, for a drug like risperidone, I might even get an adult patient up to 3 mg as quickly as possible and then move upwards from there. For an adolescent patient, I'm more likely to start at lower doses and stay on them for longer periods of time. Say, for example, I'd start off with 0.5 mg, and then shortly thereafter increase it to 1 mg, and perhaps a week after that, to go up with smaller increments and give some time between each change for the patient to adapt... And once again, due to the limited experience, if I find that the patient is not responding well after I've gotten them to that point, I often get them to see someone who's worked more in the adolescent field. — ***Quebec***

Adolescent Patients Experiencing Suboptimal Response

*I think it would be less (than adults). It's because, like, what I have seen, that they have responded better, and for some reasons, either the combination of individual counselling, family counselling plus medication, in a better therapeutic environment they did rather well. So I would say the non-respondents would be somewhere between 10% to 15 %. — **New Brunswick***

Approach to Suboptimal Response (Adolescents)

*Yeah. So that again begs the question of the other issues, diagnosis, stresses, other conditions, contributing factors, if everything is ruled out then, after going up the maximum dose, then I will add on either it could be a mood stabilizer as well, but usually an antipsychotic to combine and see how the patient will respond to it.— **New Brunswick***

*I think the adolescent tends to run through the monotherapies because you're trying very hard to kind of work with them, to establish a therapeutic alliance and to get them engaged in treatment. So they have high expectations that if they have to be on treatment that you're going to get them a drug that's invisible or seamless. And of course that's not always realistic, but they can take a few trials of monotherapy before they kind of come to terms with the fact that you have to accept the downside of treatment in order to get the upside of treatment. — **British Columbia***

Prescribing Clozapine to Adolescent Patients

*No, not under 18 years of age. — **New Brunswick***

Probably less likely. Not sure why. I don't know. I guess by the time they get diagnosed, by the time they're like, 12 they diagnosed 14, 15, then they try a bunch of meds. But then they're almost like… they just seem to be... I don't work for an EPI team, so by that point probably there'd be an early psychosis intervention team. Maybe they use clozapine. I just don't within my clients. I did try on one, but she was too sedated. Or was she an adult? No, she was a young adult. I don't know, 17.
*— **British Columbia***

*Well, adolescents don't like blood work. But if you had somebody really sick, and I've had this in my more chronic practice, I have used clozapine in adolescents, but you monitor them for the metabolic syndrome — everyone should be monitored closely, and I hope everyone is now, and I would just be on top of that, counselling for weight, diet, exercise. But I wouldn't withhold clozapine just because they're an adolescent, because they're probably really sick if they're not responding to other things if they're an adolescent. — **British Columbia***

*The very sick ones, yes. It's not probably pulled out as early on in the decisions or in their lives as in the older patient, obviously. But we do tend to turn to it in the very ill when we have to, yes. Probably 10% to 15%. — **British Columbia***

Clozapine Dosing (Higher than Recommended or Combination with Another AAP)

*No, I have not. Adolescents, I would never. There are occasions with adults where I would have, but not with adolescents. — **New Brunswick***

*Yes, again, the clozapine's nice because we have such frequent blood work that we can make small adjustments to the dosage all the way. And the blood work is really what we use as our guide. We don't look in some CPS or something that says don't exceed this. The serum level should be at 1,000 at least to get clinical response, and it shouldn't go too high or you begin to encounter bad side effects, like seizures, for example. There's a range where it's probably safe. And yes, I would push the dose in the face of continuing symptoms. — **British Columbia***

Uncertainty

Yes. In terms of combinations with mood stabilizers. I recently did a lit search for valproic acid augmentation of antipsychotics for schizophrenia, and there was very little evidence. So again, that's another area where there aren't many studies guiding us in terms of evidence-based opinions, evidence-based data. — ***Quebec***

More information about exactly monitoring and the side effect profiles, metabolic profiles of the atypicals. Yes, it'd be really lovely to have some studies on augmenting when it's, like, a combination antipsychotic therapy, be it the newer antipsychotics because the newer atypical antipsychotic,. I haven't seen a lot around that, and that would be very interesting. Maybe something with, again, the atypicals being augmented with a low dose of Haldol or those things. — ***British Columbia***

Whenever there's a new medication on the market, I think they just need to accumulate more evidence about it before. So it's really a matter of seeing people present on… I mean, like, there's been some recent studies actually talking about which is the most effective antidepressant, for example. But it took years of all of those being on the market for them to make those kind of comparisons. So I mean, I'd like to see that, and the drug companies aren't so keen on comparing themselves against each other. So it's really hard to know what's really most effective. — ***Quebec***

Well, we always will continue to learn, every day we learn something new about interactions with other medications. So that is one area which continually needs to expand. Some patients are on heart medications, on diabetes medications, and they need to be on Clozaril. So that kind of information. — ***New Brunswick***

Okay, yes. I would like to see more information on the long-term effects of atypical antipsychotics on neurogenesis and cognition. There's too many short-term studies because of the pharmaceutical industry, and not enough long-term, and I would like to see more prospective comparisons. So I would like to see more non-pharmaceutical companies, like NIH-sponsored or whatever our Canadian equivalent is, of comparisons between the atypicals and even the typicals and atypicals, studying long-term effects, prevention of relapse, improvement, cognition, neurogenesis, things like that. — ***British Columbia***

Well, I think the biggest issue is that, really, should we be using second generation of antipsychotics as first line? Given the case study saying that — and also I think there was a British study saying that the second generation really doesn't have that much advantage over the first generation in term of side effect profile or efficacy. And now with all the concerns about the metabolic side effects of the second-generation antipsychotics, that part's still not really clear to me, so which is better? Should we go back to first generation or should we be using… So should we be using a typical or atypical as first line? So that part, when I write the order, I still write the order for an atypical. But sometimes I still wonder should we really be using typicals? So that part is still confusing to me in terms of risk-benefit. Which one is better? So I struggle with that, which one to use. — ***Ontario***

I don't think there's any controversies. I think it's very clear to all the clinicians, and everybody prescribes the medication with very close monitoring and then follow-up case. So I don't think there's any controversies. But it's obviously help with more researchers and then publications and experiments have been done, that's certainly helpful. Well, if they could do some research in clinical trials on young adolescents, that probably would be helpful for me. — ***New Brunswick***

APPENDIX 4: QUOTES FROM FAMILY PHYSICIANS

Initial Treatment

*Usually atypical, because they're better tolerated and more effective. Unless it's like really acute as far as somebody's in danger we might be looking at inter-muscular Haldol or something like that. As far as oral medication, I would go with atypical. Yes, obviously they have been in use now for about, I think, more than 10 years, and they're proven to be not only effective, but also very safe, especially as far as extrapyramidal side effects and other things that we used to take Cogentin with atypicals. These ones, they don't need the Cogentin and also the risk of developing the tardive dyskinesia and other extrapyramidal side effects are much less. — **Ontario***

*Atypical. They tend to have a better side effect profile, so less chance of things like tardive dyskinesia, and it's just more commonly used these days. These specialists in the area, the psychiatrists who I might refer to for help on prescribing profiles, that would tend to be their first-line choices as well. So I tend to mirror my prescribing based on what the specialists in the area tend to do. In terms of quality of effects, they tend to have a better effect in controlling their schizophrenic symptoms. It can be used as add-on therapy for people who have major depression, so I've used that as well. Less of the side effects of tardive dyskinesia. We don't typically then have to use another medication to reduce those side effects. — **Ontario***

*Now like I said, I tend to pick the atypicals, but I can't say I have a favourite one. They all have their own uses, but basically we get familiar and comfortable and want try it. I basically start somebody on a low dose of, for example, of Zyprexa or olanzapine or Seroquel, and just go with it. It depends a little bit on, I think, the severity of their symptoms, too… I just think in the long run they're maybe a little more effective, maybe a little more, or I should say less, prone to side effects, I guess. I told you that I find them a little easier to use as well. I'm currently more familiar with it than the typical antipsychotics. — **Alberta***

*Atypical. Well, I think side effects are less. I feel more comfortable using them. I think patients tolerate them better. I think they work equally well. Side effects is the main reason, but I guess the main reason really is because I use them for depression and for mood disorders. Well, I guess back in the old days, when there were only the non-atypicals, I just never had enough opportunity to use them to get really comfortable. But since the atypicals have come out, and they seem to have so many uses, that's not the case anymore. I feel perfectly fine using the atypicals for all sorts of things. — **British Columbia***

Determining Optimal Dosing

*Well, I think primarily the effectiveness. They have to be working for the symptoms and controlling the illness. So that's the main factor. And then feeding into that, though, would be the side effects and tolerability. The person has to be able to take it, tolerating it well to want to carry on with it, too. Those are the two main drivers, actually. — **Alberta***

*Well, I like to of course control their symptoms as soon as possible because oftentimes, it creates problems at home and with the people this particular person lives with. We may also lose follow-up if we don't succeed the first time. I like to give the therapeutic dose right off the bat. Usually, I will start with, let's say, Zyprexa, 5 to 10 at bedtime or Risperdal, 2 mg at bedtime. Lately I've been using Seroquel also. But I also use these for other purposes — for example, in demented patients who are very agitated and abusive. — **Quebec***

Patient response and also general health, whether they are healthy or not. Cost and availability of samples. Many times it's people who I would deal with would not have OHIP or status in

*Canada, that's a problem. Yeah, that would be the population, otherwise the psychiatrist would deal with that. — **Ontario***

*Well, the indication for the drug and what dose is recommended, obviously; the age and the size and the weight of the patient. I usually with most medications try to start at a lower dose and titrate instead of a higher dose just to minimize tolerability issues. But as far as initial first dose, again, would be depending on the age and the weight. I guess the main two would be those two. — **Ontario***

Combination — Initial Therapy

*I'll say I don't. I've got a few people on it, but they're probably people that were already started and just led to that. And as an initial therapy, probably never. You always have to try one and see how they do. So for me, no is the answer to that. — **Alberta***

*No. I'm not as comfortable using those types of things. But again, once they see the specialist, let's say, and they might start them on those things, on combinations, and I would co-manage it. But I wouldn't do it myself. — **Ontario***

*It happens, but very rarely, whereby in one case I reached the maximum dose of Zyprexa, and then he was still symptomatic. So I lowered the Zyprexa to 10 mg and added a little bit of Seroquel to see if that has a better efficacy in controlling the symptoms. — **Quebec***

Assessment of Effectiveness of Initial Treatment

*You just really assess how their symptoms are and how they're affecting their functioning and all that. And then if they're responding, you just carry on. If they're not responding, I would probably tend to do a dose adjustment would be my initial step. — **Alberta***

I guess usually I would see them in the office and ask them about… mostly it's about their activities of daily living, how they're managing, and also getting information from the family members. So if there's any collateral information about how they're functioning.
*— **British Columbia***

*I'd probably titrate every couple of weeks or so. I would do that until either the patient was controlled or couldn't tolerate the medicine because of side effects. — **British Columbia***

*What I would do I would try to refer them to a consultant. But as I said, most of the people would make a quick referral because I'm not even sure whether they are psychotic or not or they had an episode in the past. They are a transient population, and they will be still referred. So I would not do, like, long-term ongoing follow-up. — **Ontario***

Timing of Initial Treatment

*You have to assess the patient's symptoms after treatment, after maybe a week or two, whether the symptoms are getting less than before, objectively and subjectively. — **Alberta***

Dosing Decisions (Up To and Beyond Maximum Recommended Dose)

*As I said, I would start them and refer them to a psychiatrist, so by that time I wouldn't know… I would not go all the way, I would start them and make a referral. No, no. Not more. — **Ontario***

Definitely as far as dose, I would go to the maximum dose as far as in the CPS or as far as the indication. For example, Zyprexa would be 10 mg, Risperdal would be let's say 4 mg. Again, same as the combination, I know a lot of people do that, and a lot of psychiatrists do that depending on the patient used to doing that. I usually don't do it myself. I would be

*comfortable going to the maximum dose that's recommended and indicated, and then obviously once they get seen by the specialist, they might use more than the higher dose or a combination. I have patients who are on higher than the recommended dose, and I'm comfortable. As long as the specialist has done it, I'm comfortable following those patients, but I probably wouldn't do it myself. — **Ontario***

*Yes, you get answers all over the board on that one, but I'm moderately conservative, so with Zyprexa I probably haven't done more than about 20 mg, perhaps. Seroquel, I've gone to 300 to 400 mg. And to tell you the truth, what feeds into that by the way is my sort of primary care practice, so I'll probably be getting additional psychiatric assessments or second opinions and that, if someone is not responding. And I don't really have a Risperdal comment, again, because I tend to use that one a little less. I would probably be comfortable going a little above the recommended doses. But not… well, not really high above, though. I'd probably want to get some help at that point. — **British Columbia***

*I'd rather use less. I'll be honest, I think sometimes it's better to go big or go home. So to give them the full amount may be a better approach because sometimes, while you're trying to get it right, they're suffering. But I think in general I feel safer. — **Ontario***

Patients Experiencing Suboptimal Response on Recommended Dosing

*I would say the success rate is about 70% with one agent, and this is at an average or just above average dose. If you go up to the maximum dose, you may go to 80% to 85% success rate. The other 15 or 20, like I said, we have to probably use two agents. So usually, like I said, I will go down a little bit from the maximum and add another agent. — **Quebec***

*Unfortunately, with psychosis and schizophrenia and these types of illnesses, they do relapse regularly. The percentage I would say, I'm just guessing, but I would say that it's 50% of the time. — **Ontario***

*I think low if they keep on the medicine. The problem is a lot of them feel better and then they stop or they try to lower the dose. And then their symptoms come back. That's the problem. I don't think it's that the drugs don't work, but in my cases I guess they just stop the medication. I would say probably about 20%. — **British Columbia***

*It's a good question. For me, again, the difficulty in that answer is like I said, 90% of the people I see are stable on what they're on. So maybe only about 10%, I guess is my real guess, basically. I think actually a lot of the times it was the comorbidities. A lot of these guys dabbled with drug use and things like that, which I think is part of their disease, or maybe it causes their disease too, sometimes. So I guess that was one factor I could think of is overlapping drug use. Things like their social support network too would be a bit of a factor, too. Homeless people or people out on the street more or less have no social support tend to do a little worse, I think, than the people who are at home and have a supportive family. — **Alberta***

Approach to Patient Suboptimal Response

*I would probably switch to something else that's available, another atypical agent. Well, with Seroquel XR we do use it for… it has new indications for depression. So in that sense I can use it in combination with something else. But I haven't really had much experience in using atypicals in combinations as such. Mostly single, mostly just by themselves. — **British Columbia***

*Usually I start to switch antipsychotics first. And then I try that for maybe a month or two, if that doesn't get better, I refer to a psychiatrist. I would try a maximum of two agents after the first one. I do not use combination therapy. — **Alberta***

*Well, if they're tolerating I'll tend to push the dose a little bit, so I might go up to one and a half times the dose, roughly speaking; if they're tolerating it. If they're not tolerating it, I will do a switch, actually, and just try one of the other. And usually, it would be another atypical. — **Alberta***

*I think if the patient is tolerating the medication very well, I would think that you would increase the dose, for sure. Although, again, I probably wouldn't do it myself and I would do it with the help of the psychiatrist. But that's one way. The other way would be to add second agents, combine agents together to increase efficacy. — **Ontario***

*We need to make sure that they're taking their medication. So I may ask him to show me the bottle. I may call the pharmacy. I may ask the family if he's compliant with taking his meds every day. And if I am convinced that he is taking them, then obviously we have to either increase the dose if they're only taking the average dose, or if they're taking the near-maximum dose, I may add a second one or switch to another antipsychotic. — **British Columbia***

*I guess if there's a problem, you know what you've given, what's there. You can see the response, as opposed to… I think some of the side effects are potentiated probably with more than one drug on board. I think patients also resist more than one, again you start throwing a whole bunch of drugs at them. — **Ontario***

Prescribing Clozapine

*I think it's a good drug, actually. It needs some monitoring. I've only got guy on it, so I don't have a whole lot of experience there. But I think it's a reasonable, and actually a very good back-up if need be, actually. But in the primary care setting that I belong in, that would sort of be one of those things where from my perspective, I'd be getting a psychiatric second opinion on that one. But certainly I think that's an okay choice and usually a good choice, if nothing else has been effective. I wouldn't go right to clozapine. For me probably it's more my experience level, but I'd certainly try the other atypicals before I went to clozapine. Again, I think it can be an excellent choice on the right individual. — **Alberta***

*No. I have some patients who are taking it, but they have been prescribed by their psychiatrist. I just renew it for them and I watch their blood in terms of CBC and biochemistry to make sure there's no side effects in that respect. But they also usually are followed by psychiatrists who see them every six months. — **Quebec***

*If they've gone through probably about three other antipsychotics and just didn't respond to it, then that might be one where someone might [inaudible] that. If they didn't respond to higher doses of a combination therapy or if they weren't tolerating a higher treatment either, like if they just weren't going to take it or couldn't take it, and it's combination and they couldn't take it or wouldn't take it, couldn't tolerate it, I'd probably consider trying a different combination, and then if that didn't work, then the clozapine would be probably the next one. — **Alberta***

*Well, most important would be if they've had a good response to it in the past. I think I would tend to use it with patients that I guess have a more severe form of schizophrenia, more frequent psychotic episodes and so on. I'd probably try one of the ones I'm comfortable with first because I would sort of reach for the ones I'm most comfortable with. If that doesn't work, then I'd probably go to clozapine. If that didn't work, maybe try a combination and then refer at that point. — **British Columbia***

*I think the dosing is pretty simple, and generics are available. So a lot of times they could be cheaper. The doses, you can titrate it once, twice to three times a day. So there's flexibility in that use. — **British Columbia***

*Well, I think the advantages, I think it can be effective if the other things have failed. It does have a different degree of effectiveness, actually, so I don't know if "potent" is quite the right word, but basically people might respond to that that haven't responded to other treatment. — **Alberta***

*Yes, decrease in white blood cell count. Yes, that's another one. So usually we would need to measure the white blood cell count as a baseline before you start treatment and then probably every week, as they're on treatment. And also after you stop, you still have to monitor it because the drug stays in your system for a few weeks. — **British Columbia***

The disadvantage is it needs monitoring. I'm not sure how critical. I think it gets overrated or overplayed, in my opinion, but you can't argue with the recommendations and the potential for risks and side effects and all that. That means more monitoring, I think, so that's an issue that comes up sometimes.

*Disadvantages, I guess I worry about side effects more with that one. Most worrisome, well, GI side effects I worry about, neurological side effects. I think there's weight gain as well. That's it. — **British Columbia***

Treating Adolescents

*For adolescents, I tend to refer them sooner. Usually I give them the antipsychotic, and if they fail to respond or have a suboptimal response, I refer them right away, but in the meantime, while they're waiting to see a psychiatrist, maybe I play around a little bit with the dosing. Refer them sooner. — **Alberta***

*Unfortunately, I don't have that many. I have a few, and in that case, in that age group, obviously parents are involved and everything, I don't think that — obviously, I would follow them — but definitely they would be seen by a psychiatrist fairly quickly. Yes, I wouldn't wait to try drugs and see efficacy before deciding if they need to see a psychiatrist. Usually parents insist that they want to see a psychiatrist. And if they didn't, I think at that age group, because they're going to be on medication and all that other stuff, I think definitely I would have a co-managed situation with a psychiatrist. I wouldn't do it myself, on my own. — **British Columbia***

*I do have a few. They're not that common, but I do have a few. But again, all of them have a psychiatrist and are regularly followed by a psychiatrist. — **Ontario***

*I don't think I would go higher than normal. I may refer them to a psychiatrist. Or I may, like I said, give them a low dose of another antipsychotic. — **Quebec***

*I think mainly just start low and increase even slower. And I guess the atypical antipsychotics, they all have metabolic side effects as well. And so I know a lot of teens would be worried about their weight because the weight gain would be a big issue to them. And so they need to monitor the blood sugar, cholesterol, and their weight. — **British Columbia***

*If they're really young, 12 or 13, I'd probably be a bit more conservative. I don't have an age in my mind, I'm just kind of assuming here. But if someone's close to 18, I'd start at a full adult dose and work up to the next highest. So I think the general answer, I'm not going to work up to the highest recommended dose if need be. I probably, in an adolescent, wouldn't go above the recommended adult dosing; again without getting a second opinion. — **Alberta***

*I usually go with Risperdal first line. I may prescribe let's say 5 mg to start to make sure we get full control of their symptoms. And then once they're doing okay, we may try to go down on the dose just to find out the ideal dose without giving too much. — **Quebec***

*Well, I would give it probably two to four weeks in between titrations. Using Zyprexa, I guess I'd probably start in the 5 mg range, and maybe go up to 20. And I'd probably rely a lot on the family to give me feedback on how it's working. — **British Columbia***

*Yes, the main factors — again, it goes back to the effectiveness, like it has to be helping their symptoms and doing something — and so that's the main factor. And then again, the other factor that's key is the tolerability. So they have to be able to be tolerated enough to keep taking the pills, which is a challenge sometimes. But yes, those two things. — **Alberta***

*Combinations, no. Occasionally, I use something else with an antipsychotic, like maybe a sedative like a sleeping pill or something very occasionally. But I would tend not to use two antipsychotics together because then you don't know really which one's helping them or not when you start with two. — **Alberta***

Uncertainty

*I think we should have more CMEs about the combination use of atypical antipsychotics. I mean, just thinking logically, like if one atypical antipsychotic already has a number of metabolic side effects, I'm just really concerned about using them in combinations. — **British Columbia***

*I would still prefer if a rep would come and talk to me and explain about anything, any new studies that have been done, any new indications for the molecule. But I also want to see some scientific proof… — **Quebec***

*… more evidence regarding safety and efficacy, and especially gearing towards the general practice. I know psychiatrists they use a high dose, but GPs, we tend to back off a little bit because lack of safety and sometimes I feel a little bit uneasy about prescribing higher dose. I'd like to see some evidence about it. — **Alberta***

*I guess sometimes when people are complex cases or patients are on multiple medications that would be drug interaction, things like that, would concern me. — **Ontario***

APPENDIX 5: ABBREVIATIONS

AAPs	atypical antipsychotics
ACP	Advisory Committee on Pharmaceuticals
CAC	COMPUS Advisory Committee
CERC	COMPUS Expert Review Committee
CME	continuing medical education
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
DPAC	Drug Policy Advisory Committee
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
EPI	early psychosis intervention
EPS	extrapyramidal symptoms
GP	general practice physician
ICD-10	International Statistical Classification of Diseases and Related Health Problems
OHIP	Ontario Health Insurance
OUWG	Optimal Use Working Group
TAP	typical antipsychotics
TD	tardive dyskinesia
US	United States

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