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Préface / Foreword

Evaluating Antipsychotic Medications: Predictors of Clinical Effectiveness

Report of an Expert Review Panel on Efficacy and Effectiveness

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Au cours des dix dernières années, les antipsychotiques atypiques (olanzapine, quétiapine et rispéridone) sont devenus des premiers choix pour amorcer et maintenir un traitement de la schizophrénie. Dans de nombreux cas, ces antipsychotiques ont remplacé les neuroleptiques typiques, associés à une incidence fréquente d'effets secondaires, en particulier le parkinsonisme et la dyskinésie tardive.

Chaque compagnie pharmaceutique qui produit des antipsychotiques atypiques a effectué de nombreuses études pour tenter de démontrer la supériorité de son médicament par rapport à ses concurrents. Plusieurs de ces études sont malheureusement de trop courte durée, étant donné que la schizophrénie et les autres psychoses exigent un traitement à long terme. Néanmoins, ces études ont permis d'obtenir plusieurs données intéressantes et probantes. Cependant, le clinicien ne se base pas seulement sur des données d'études. L'expérience clinique, qui permet de suivre des patients de façon prolongée, a aussi beaucoup d'importance dans le choix d'un antipsychotique. Cet article a l'originalité de tenir compte de ces deux aspects pour mieux prescrire des antipsychotiques atypiques.

Over the course of the last decade, atypical antipsychotic medications (olanzapine, quetiapine, and risperidone) have become first-line choices for acute and maintenance treatment for schizophrenia. In numerous cases, these antipsychotics have replaced typical neuroleptics, which are associated with a high incidence of adverse effects, particularly parkinsonism and tardive dyskinesia.

Each pharmaceutical company that produces an atypical antipsychotic has supported numerous studies in an attempt to demonstrate the superiority of its agent compared with its competitors. Many of these studies are, unfortunately, too brief in duration, given that schizophrenia and the other psychoses require long-term treatment. Nevertheless, those studies have yielded interesting and evidence-based data. The clinician cannot, however, rely entirely on data from studies. Clinical experience, which allows clinicians to follow patients for prolonged periods of time, is also important in choosing an antipsychotic medication. This article takes the refreshing approach of considering both of these aspects to guide more appropriate prescription of the atypical antipsychotics.

Introduction

When faced with a decision about patient care, clinicians have to consider several variables. Where should the patient be treated? Is the patient capable of being an active part of the care team? What types of lifestyle modifications might be helpful? Is pharmacologic therapy appropriate? Which agent or agents should be prescribed?

This last question raises a host of new variables. Evidence-based medicine dictates that physicians base their decisions on relevant data published in the peer-reviewed medical literature. Ever since "evidence-based medicine" became the buzzword of medical care, however, the issue of what constitutes relevant data has been debated. Can clinical trials be considered to be representative of everyday clinical practice? Because of the many differences between these treatment scenarios, many experts have sought to differentiate between efficacy and clinical effectiveness.

In 2002, there was no consensus on the differences between efficacy and clinical effectiveness or how each fits into the overall picture of care. Based on the conclusions of a round-table meeting of Canadian experts in psychiatry, this report attempts to provide an up-to-date, Canadian perspective on this complex issue as it pertains to antipsychotic medications. The specialists, Dr Chekkera Shammi, Dr Sean Flynn, Dr Roger McIntyre, and Dr Kiran Rabheru, each brought his unique perspective to the deliberations. Dr Rabheru specializes in treating psychiatric problems in older adults, Dr McIntyre's chief interest is mood disorders, and both Dr Flynn and Dr Shammi have a particular interest in schizophrenia.

This panel of experts constructed a comprehensive model that best describes the concept of clinical effectiveness. This model is then used to examine the various applications of the atypical antipsychotics (clozapine, olanzapine, quetiapine, and risperidone).

Efficacy and Clinical Effectiveness: Definitions

Efficacy is defined by *Dorland's Illustrated Medical Dictionary* as "the ability of an intervention to produce the desired beneficial effect in expert hands and under ideal circumstances" (1). This definition was adopted by one of the earliest published reports dealing with the efficacy vs effectiveness debate. In 1985, the US National Institute of Medicine (NIM) published a report on the assessment of medical technologies (2).

The NIM paper explained that efficacy is best measured by randomized, clinical trials. These trials are designed to test an intervention under circumstances as close to ideal as possible. Inclusion and exclusion criteria are precisely developed and enforced to ensure that the patient population is as homogeneous as possible. This is done as an attempt to minimize the risk of variables' jeopardizing the statistical strength of the results. The limitations are obvious: it is logistically and economically impossible to test any given intervention in the full spectrum of patients in which it might be used, which sometimes makes it difficult for a clinician to determine the relevance of a well-designed study to a particular patient who would not have fit that study's inclusion criteria.

Effectiveness is defined by *Dorland's* as "the ability of an intervention to produce the desired beneficial effect in actual use" (1). This too was essentially the assertion of the NIM paper, which stated that surveillance and database analysis were the best methods of assessing the effectiveness of a given intervention (2).

Clinical effectiveness is an inclusive concept that builds on the ideas of such efforts as the NIM paper and those that followed it. Essentially, it can be broken down into 4 components: efficacy, tolerability and safety, function, and acceptability. All 4 of these components, or domains, interact and combine to provide us with insight into a particular intervention's clinical effectiveness. Figure 1 is a graphic representation of this concept.

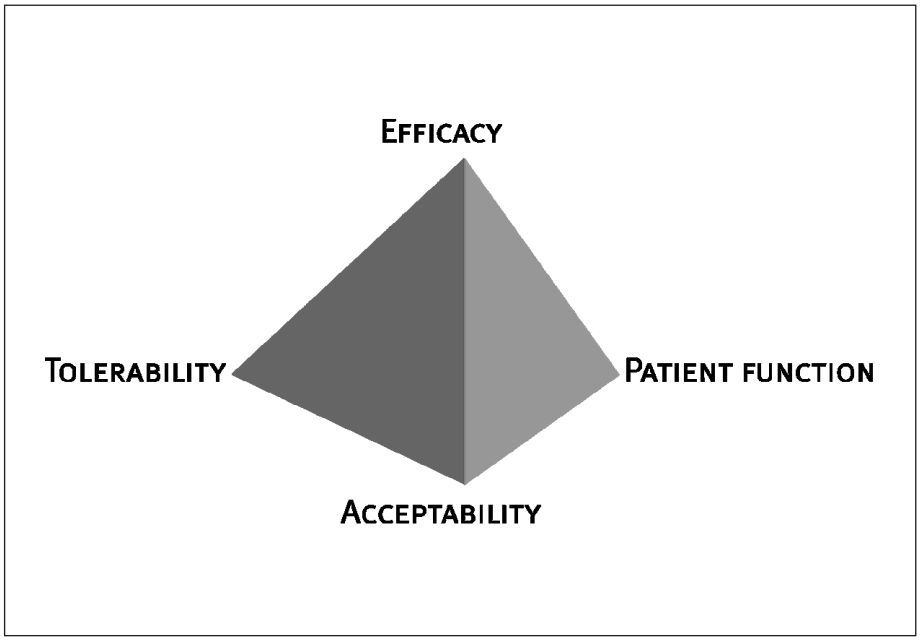
Clinical Effectiveness Domains

There are a number of important variables that combine to make up each of the 4 domains of clinical effectiveness.

- In the domain of efficacy, for example, the most important variables are symptom relief, relapse rates, and comorbidities. The efficacy domain is closely linked to appropriate dosing.
- In the tolerability and safety domain, the most relevant elements are side effects, safety, and ease of use.
- Function, the third domain, includes activities of daily living and quality of life. These are all elements that can be quantified and measured in randomized, clinical trials or observational studies.
- Acceptability, the fourth domain, is a looser term; it is affected by the other 3 domains and refers not only to the acceptability of a drug to a patient but also to the care team. Compliance is a major factor in judging an intervention's acceptability. If the patient doesn't take the medication as prescribed, the efficacy and tolerability no longer matter. Put another way, if an agent has low rates of compliance, it is somehow unacceptable to the patient.

Overall, although clinical effectiveness incorporates domains that are quantifiable in their own right, the clinician with standard tools can also measure clinical effectiveness itself. The Clinical Global Impression (CGI) scale is a well-known tool that is simple and quick to administer. It is the simplest means to gain insight into and quantify the overall clinical effectiveness of an intervention. The Positive and Negative Syndrome Scale (PANSS) is commonly used to assess mental status and the impact of therapeutic intervention.

Figure 1 The 4 domains of clinical effectiveness



Clinical Effectivness of Interventions in Psychiatric Medicine

The efficacy and effectiveness issue has been formally debated within the community of psychiatric medicine. In the June 1998 issue of *Psychiatric Services*, a point–counterpoint debate was published (3). Dr. Gerard Hogarty extolled the virtues of randomized, controlled clinical trials as the gold standard of evidence-based medicine, while Dr William Summerfelt and Dr Herbert Meltzer argued this type of efficacy trial, while essential as a foundation for clinical knowledge, has limited applicability to clinical practice and should be supplemented with more reality-based "effectiveness" research to better predict real-world outcomes.

In the spirit of the latter argument, the following section will break down the available literature to discuss each of the 4 atypical antipsychotics with respect to each of the 4 domains of clinical effectiveness: efficacy, tolerability and safety, function, and acceptability.

Clinical Effectiveness of Clozapine

Clozapine, the first atypical antipsychotic drug, is currently indicated only for the management of treatment-resistant schizophrenia (4).

Efficacy in Schizophrenia. Clozapine is indeed an efficacious drug. It has been studied clinically in a number of different patient populations (mostly in schizophrenia). A 1999 metaanalysis of randomized, controlled trials showed that clozapine was superior to the traditional antipsychotics in managing the symptoms of schizophrenia (5). This may include a direct effect on negative symptoms, which was demonstrated in a trial using clozapine in patients with minimal positive symptoms (6). Where clozapine truly sets itself apart from the other atypical antipsychotics, however, is in the treatment of schizophrenia refractory to other medications. Both clinical (7) and observational (8) studies have shown that refractory patients can be well maintained on this agent. This is reflected by the Canadian schizophrenia guidelines, which recommend its use in refractory disease (after a minimum of 2 other agents have been tried [9]).

Dosing. Dosing is an important consideration in efficacy as well. The therapeutic plasma concentrations of clozapine for treatment-resistant patients are in the range of 350 to 504 ng/mL (10). The typical dosage required to achieve the therapeutic effect is between 300 and 500 mg daily in divided dosages (4). Smaller dosages (200 to 300 mg daily) may be enough for some patients. To avoid daytime drowsiness, the dosage can be administered at bedtime.

Efficacy in Other Populations. Owing to the safety limitations of this drug (see below), it has not been as widely studied in other applications (that is, bipolar disorder, dementia) as have the other atypical antipsychotics. That being said, there is some case-report evidence that clozapine is effective as add-on therapy in patients with bipolar disorder poorly controlled on mood stabilizers (11).

Tolerability and Safety. The clinical effectiveness of clozapine is greatly hampered by its safety profile. There is a well-recognized risk of life-threatening blood dyscrasias (that is, agranulocytosis) with this medication (4). This is the major reason why clozapine is reserved for refractory cases. The possibility of agranulocytosis dictates that patients taking clozapine undergo regular blood monitoring and enroll in a patient surveillance program. In some cases, it is a difficult, if not impossible, to follow these patients adequately. Certainly, clozapine monitoring makes this agent the most problematic of the atypical antipsychotics in terms of ease of use.

There is also a concern with cardiovascular toxicity with clozapine (4). An advisory issued by the drug's manufacturer and circulated by Health Canada in 2002 reported that an analysis of safety databases suggests that the use of clozapine is associated with an increased risk of myocarditis especially during, but not limited to, the first month of therapy (12). Further, the report lists pericarditis, pericardial effusion, cardiomyopathy, heart failure, myocardial infarction, and mitral insufficiency as having been reported in association with clozapine use (12).

Orthostatic hypotension (with or without syncope) can occur with clozapine (estimated incidence 1 in 3000), usually in the initial titration period (4). Rapid titration should therefore be avoided.

In terms of tolerability, weight gain may also be a consideration. A randomized, comparative trial in 33 patients with schizophrenia showed that substantially more patients taking clozapine (7%) gained weight than those taking haloperidol (1%) (13). Fifty-eight percent of patients gained at least 10% over baseline while taking clozapine (14).

It is thought that the issue of weight gain may be linked to an association between clozapine and diabetes (14) The hypothesis suggests that the increase in adipose tissue leads to insulin insensitivity, glucose intolerance, and, if severe enough, diabetes.

Clozapine has been shown to cause less tardive dyskinesia (TD) than traditional agents (15). TD is one of the most frequently encountered and distressing side effects of traditional antipsychotic treatment.

A retrospective chart analysis has also demonstrated that low-dosage clozapine is generally well tolerated by elderly patients with dementia (16), while another small observational study showed that, even at low dosages (6.5 to 37.5 mg daily), severe adverse effects have occurred with clozapine in elderly patients with psychosis and dementia (17).

Function. Assessing the impact of clozapine on daily function is somewhat problematic. On the one hand, clozapine's favourable impact on symptoms can improve the patient's activities of daily living. The Veterans Affairs (VA) Cooperative Study of Clozapine in Refractory Schizophrenia found that clozapine therapy was associated with a 26% increase in Quality of Life Scale scores (18).

Cognitive function is especially important in patients with psychoses and is considered "a powerful predicator of the value of novel treatments in the improvement of social and vocational change." In terms of cognitive function, a metaanalysis of clozapine studies showed that there was strong evidence that clozapine improves attention and verbal fluency and moderate evidence that clozapine improves some types of executive function. No conclusions were drawn about the effects of clozapine on working memory and secondary verbal and spatial memory, as the analysis of these factors was inconclusive (19).

Significantly, with clozapine, blood monitoring must be performed every 1 or 2 weeks to watch for blood dyscrasias; this can be unacceptably cumbersome and invasive to the patient's quality of life.

Acceptability. The acceptability of clozapine is enhanced by its efficacy in symptom relief and its relatively low incidence of TD. Patients will often feel better and are therefore more likely to continue on the medication, enhancing the acceptability of the drug. For many patient and care team members, however, acceptability is compromised by clozapine's safety and tolerability concerns and the impact of the monitoring system on patient quality of life.

Summary. Clozapine's clinical effectiveness must be evaluated on a case-by-case basis. The key element of the effectiveness domains in this case is the issue of blood monitoring. For some, the regular monitoring could represent an opportunity to provide better follow-up care and enhance the agent's clinical effectiveness. For other patients or health care professionals, however, weekly blood tests will make the intervention clinically ineffective because of aspects of time and resource use.

Clinical Effectiveness of Risperidone

Risperidone is also indicated for the acute and maintenance treatment of schizophrenia and related psychotic disorders (20) and has also been studied in bipolar disorder and dementia.

Efficacy in Schizophrenia. The efficacy of risperidone in schizophrenia is well documented. Studies have included such populations as first-episode schizophrenia (21), treatment-resistant patients (22), and children (23). It has been evaluated in head-to-head trials with olanzapine in patients with schizophrenia (24) and clozapine in patients with treatment-resistant schizophrenia (22). Risperidone and olanzapine were found to be equally efficacious at all points except at 6 months, where risperidone was superior in terms of reduction of psychotic symptoms (24). In the treatment-resistant study, risperidone was found to be as effective as medium dosages of clozapine (22).

Efficacy in Bipolar Disorder. In bipolar disorder, risperidone has been shown to be efficacious as monotherapy and as an add-on therapy to mood stabilizers (25) and, in a retrospective chart review, showed that it may be effective in controlling mania (26).

Efficacy in Elderly Psychoses. Risperidone has been widely studied in dementia as well. In a comparative study with olanzapine, the investigators determined that both agents may be effective in improving functioning in elderly patients with dementia and psychosis (27). Risperidone has also shown benefit in dementia associated with AIDS and Alzheimer's disease (28,29).

Dosing. In terms of dosing, clinical experience with risperidone has led to the recommendation that it be slowly titrated to the target dosage of up to 4 mg daily for most patients (30). In elderly patients the dosage should not generally exceed 2 mg daily. It is important to note that the dosing for dementia patients is much lower than for other psychotic disorders. Target dosage for these patients should be 1 mg (range 0.5 to 1.5 mg) daily. Higher dosages may result in higher risk of extrapyramidal symptoms (EPS) and lower efficacy.

Tolerability and Safety. Risperidone has demonstrated less EPS and TD than the conventional antipsychotics (31). However, higher dosages of risperidone have resulted in

levels of EPS similar to the typicals. Weight gain is a concern with risperidone, although to a lesser degree than olanzapine and clozapine, as demonstrated in a head-to-head study in adolescents (32). One of the most common adverse effects attributed to risperidone therapy is insomnia (20).

Perhaps the most overlooked effect reported with risperidone is an increase in prolactin levels. Hyperprolactinemia can be associated with a variety of side effects, including amenorrhea, galactorrhea, sexual dysfunction, breast engorgement, and osteoporosis (33–35). Elevated prolactin with no side effects, however, does not appear to be significant.

When using risperidone, the clinician should have an elevated index of vigilance for these symptoms. There have also been reports of absence of ejaculation in risperidone-treated patients, which remains unexplained, but may be due to the agent's relatively potent alpha-adrenergic antagonism (36).

Function. Risperidone is an agent that has provided symptom relief and quality-of-life enhancement in many populations. Daily functioning, as a result, can improve greatly with this therapy. An ongoing study, the Risperidone Outcomes Study of Effectiveness (ROSE) includes quality of life measures in its outcomes (37). The results of this trial are not yet available.

A metaanalysis examining the effects of atypical antipsychotics on parameters of cognitive function showed that risperidone has relatively consistent positive effects on working memory, executive functioning, and attention, whereas changes in verbal learning and memory were inconsistent in clinical trials (19).

With risperidone, there is the potential for adverse effects that can detract from the agent's overall clinical effectiveness. Gynecomastia and sexual dysfunction can have a deleterious effect on quality of life.

Acceptability. The acceptability of risperidone can vary greatly. The efficacy of the drug has been demonstrated in various populations, but EPS- and prolactin-related side effects can make this agent unacceptable for certain patients.

Summary. Risperidone is an agent that can be clinically effective in a large number of patients. Side effects can, however, jeopardize clinical effectiveness, and each patient should be assessed individually before selecting risperidone.

Clinical Effectiveness of Olanzapine

Olanzapine is indicated for the acute and maintenance treatment of schizophrenia and related psychotic disorders (38) and has been widely studied in many populations of patients with schizophrenia, bipolar disorder, and dementia.

Efficacy in Schizophrenia. The efficacy of olanzapine in symptom relief for schizophrenia has been documented in a number of clinical trials and observational studies in a number of populations, including in those intolerant or resistant to risperidone (39), in those switched from clozapine (40), and in those refractory to other antipsychotics (41). There have been no trials investigating the efficacy of olanzapine vs clozapine. It has, however, been compared with risperidone in schizophrenia.

Efficacy in Bipolar Disorder. Olanzapine has also shown efficacy in alleviating the symptoms of bipolar disorder, including established efficacy as monotherapy, as adjunctive therapy to mood stabilizers (42,43), and as therapy for acute mania and bipolar depression (44). A double-blind study comparing olanzapine with divalproex in monotherapy showed no significant differences in efficacy variables between the 2 agents, but olanzapine was associated with higher incidence of somnolence, weight gain, edema, rhinitis, and speech disorder (45).

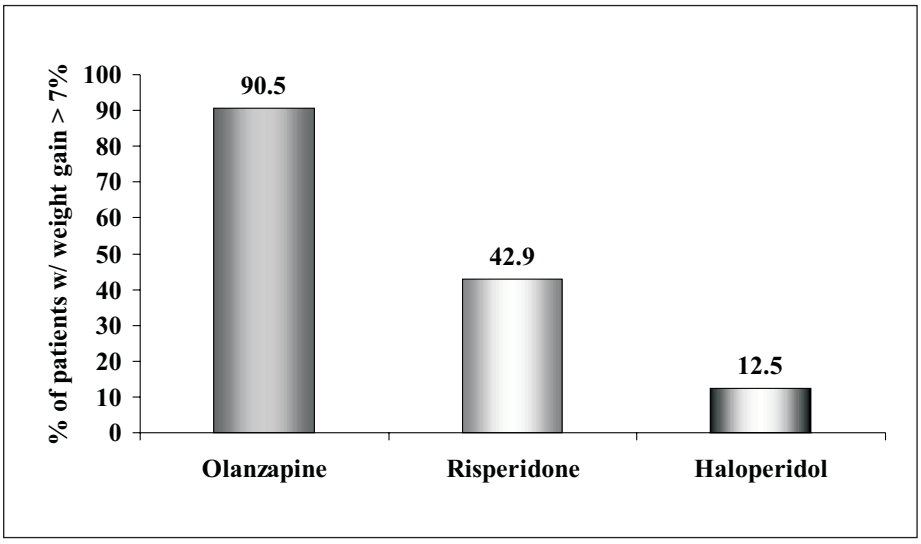
Efficacy in Elderly Psychoses. In patients with dementia, investigations have also demonstrated that olanzapine can be efficacious. These investigations have included patients with psychotic and behavioural problems in Alzheimer's disease (46), those with anxiety associated with Alzheimer's disease (47), and in patients with Parkinson's disease with or without dementia (48). A preliminary investigation into the utility of olanzapine in dementia with Lewy bodies ($n = 8$) showed that it was not superior to conventional antipsychotics and was not tolerated, even at the lowest available dosage, in 3 of the 8 patients (49)

Dosing. The plasma concentration of olanzapine that predicts response in schizophrenia has been reported as equal to or greater than 23.2 ng/mL (50). The typical dosages fall between 5 and 20 mg daily (51). It is once again important to note that the dosing for dementia patients is lower than other psychotic disorders. Target dosage for these patients should be 5 to 10 mg daily to minimize risk of EPS and enhance efficacy.

Tolerability and Safety. The major precautions with olanzapine in terms of safety and tolerability are its tendency to cause drowsiness (especially at higher dosages) and its propensity for weight gain (38). Weight gain in schizophrenia is particularly important in that patients most often require chronic therapy and compliance can be greatly jeopardized by this adverse effect (51). For safety reasons, the possibility of somnolence may preclude the use of olanzapine in patients where alertness is required for occupational or other reasons. These problems can, however, be minimized by lowering the dosages or by concentrating the dosages in the evening. In some cases, somnolence may even enhance clinical effectiveness in patients where insomnia or other sleep disorders are an issue, particularly when olanzapine is taken at bedtime.

The product monograph for olanzapine indicates that the mean weight gain for patients treated with 5 to 20 mg of olanzapine daily is 5.4 kg over the first 6 to 8 months of treatment (31). The aforementioned study in adolescents, however, showed that, in this patient group, olanzapine-associated weight gain was significantly greater than that seen in other populations and is greater in this population than weight gain associated with risperidone or haloperidol (32). Average weight gain was 7.2 kg (11.1% of body weight) in the

Figure 2 Weight gain with olanzapine, risperidone, and haloperidol (29)



olanzapine group, 3.9 kg (6.6%) in the risperidone group, and 1.1 kg (1.5%) in the haloperidol group. In terms of extreme weight gain, 90% of adolescents in the olanzapine group exhibited a greater than 7% increase in weight, compared with 43% of the risperidone group and 13% of the haloperidol group (Figure 2).

Olanzapine's increased propensity to cause weight gain may also have an impact on the relative risk of diabetes. A chart analysis in 33 946 Quebec patients showed that the relative risk of developing diabetes was 20% higher for patients treated with olanzapine, compared with those treated with risperidone (52).

Owing to the risk of orthostatic hypotension with olanzapine, caution should be used when considering this agent for patients with cardiovascular problems (38).

Other adverse effects, including TD and EPS, appear to be similar to other atypical antipsychotics and less frequent than the traditional antipsychotics. They are more common at very high dosages (53).

Function. The efficacy in symptom reduction demonstrated by olanzapine in various patient populations can help enhance functioning and quality of life. A study comparing olanzapine and haloperidol, for example, showed that olanzapine therapy was associated with a 50% improvement in the Quality of Life Scale during acute treatment and a 69.5% improvement during maintenance therapy (54).

In terms of cognitive function, preliminary evidence presented in a metaanalysis of atypical antipsychotics suggested that olanzapine improves verbal learning and memory, verbal fluency, and executive function but not attention, working memory, or visual learning and memory (19).

In some patients taking olanzapine, somnolence can be an intolerable side effect. Excessive weight gain can also have a deleterious impact on patient self-esteem and quality of life.

Acceptability. The acceptability of olanzapine is generally quite good. It is efficacious in many populations and is, for the most part, well tolerated and safe. Somnolence may be a factor that limits acceptability for some patients but enhances it in others. Excessive weight gain with olanzapine is the largest impediment to acceptability—particularly for the patient—and should be kept in mind, especially in those patients with cardiovascular risk factors.

Summary. Assessing the clinical effectiveness of olanzapine, like any medication, should be done with an individual patient in mind. For many, a physician might predict that olanzapine will be clinically effective for a particular illness. For others, fear of weight gain may limit its acceptability and, hence, its clinical effectiveness.

Clinical Effectiveness of Quetiapine

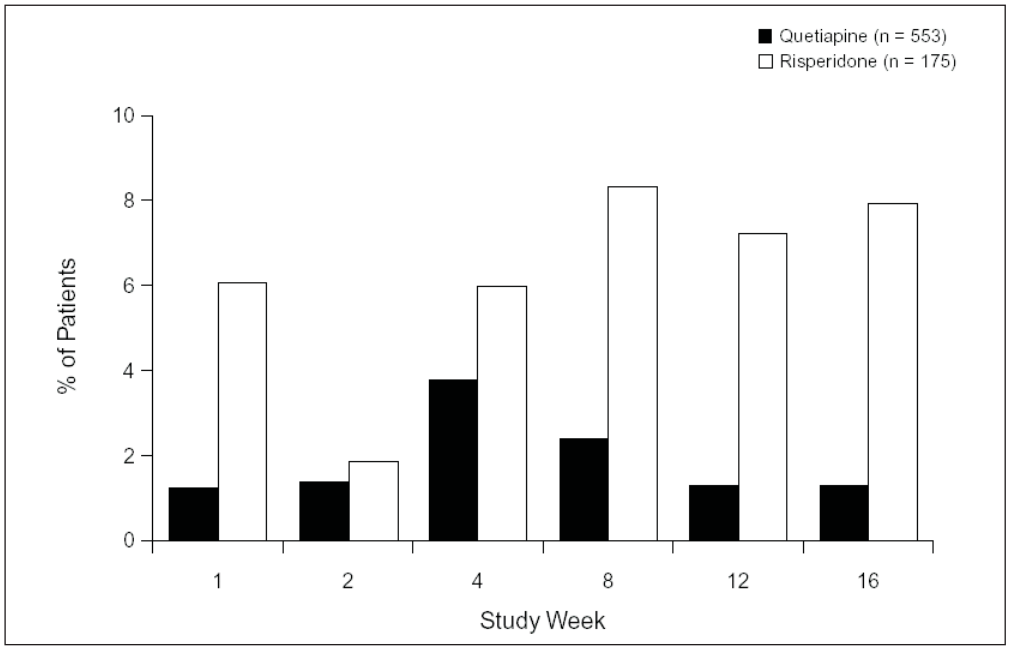
Quetiapine is indicated for the management of the manifestations of schizophrenia (55). It has also been widely studied in bipolar disorder and elderly psychoses. As the newest agent among the atypical antispychotics available in Canada, the evidence accumulated for quetiapine is less than that for risperidone or olanzapine. While further study would be informative, particularly in longer-term use, there exists already a growing body of evidence for quetiapine in the various domains of clinical effectiveness.

Efficacy in Schizophrenia. As is the case with the other atypical antipsychotics, the efficacy of quetiapine has been well established in the literature. In schizophrenia, quetiapine has shown benefit in patients across all symptom domains (positive, negative, cognitive, and behavioural) (56,57). Quetiapine has demonstrated efficacy in first-episode schizophrenia (58–60), in schizophrenia in children and adolescents (61), in partial responders (62), and in long-term treatment (63).

In first-episode patients, quetiapine has demonstrated efficacy in a 12-week open trial in patients aged 16 to 45 years, newly diagnosed with schizophrenia or schizoaffective disorder and naïve to antipsychotic therapy (59). Patients experienced a significant mean reduction in each of the outcome measures (CGI and PANSS positive, negative, general, and total) without any increase in TD or EPS.

In children and adolescents, the efficacy of quetiapine has been examined by retrospective chart review of 14 patients

Figure 3 Incidence of EPS: quetiapine and risperidone (64)



(including 3 experiencing their first episode) treated in a community mental health centre (61). Of the 14 patients on quetiapine (average dosage 308.9 mg daily), 11 were rated as much improved or very much improved on the CGI, and none discontinued therapy because of adverse events.

In the trials examining partial responders, quetiapine was compared with haloperidol in 288 patients (62). The investigators found that, after 8 weeks, those patients titrated to quetiapine 600 mg daily had significantly greater responses in terms of mean PANSS, compared with haloperidol 20 mg daily (–11.5 vs –8.87, respectively).

As far as long-term data are concerned, a metaanalysis of 4 open-label extension quetiapine trials ($n = 674$, average dosage 472 mg daily) showed that the significant improvements in both positive and negative schizophrenia symptoms, as well as the tolerability benefits of quetiapine monotherapy, are maintained over the long term (endpoint 130 weeks) (63).

Quetiapine has also been evaluated in a head-to-head trial with risperidone in patients with schizophrenia (64). Both agents were equally effective in improving psychotic symptoms. However, quetiapine was significantly superior to risperidone in improving depressive symptoms.

Efficacy in Bipolar Disorder. In bipolar disorder, quetiapine has demonstrated efficacy alone or as add-on therapy (65–73). Quetiapine has been shown to be efficacious in patients refractory to other treatments (66,68), in rapid-cycling bipolar disorder (69), in those with concurrent substance abuse (70), in adolescents (71), and in children (72).

The most significant results for quetiapine in bipolar disorder come from a randomized, placebo-controlled study in 170 patients hospitalized for an acute manic episode. The investigators found that patients who received quetiapine in addition to mood stabilizers had significantly better response rates, changes in the Young Mania Rating Scale and CGI scores, and remission rates over the 21-day study (73). Withdrawal rates for adverse events in this study were actually slightly higher for the placebo group.

Efficacy in Elderly Psychoses. Quetiapine was evaluated in a 52-week study examining a large group of elderly patients with various psychiatric problems, including psychosis associated with Alzheimer's disease (42%), Parkinson's disease (22%), or schizophrenia (17%) (74). Quetiapine demonstrated significant reduction in hostility and aggression and significant improvement in positive and negative symptoms.

Quetiapine has also shown efficacy in elderly patients with psychoses and Parkinson's disease (75) and in Parkinson's disease with Lewy body dementia (76).

Dosing. Clinical experience is showing that the most appropriate target dosages are 400 to 600 mg daily in first-episode psychoses, 600 to 800 mg daily in established schizophrenia, 600 mg daily in acute mania, and 100 to 200 mg daily in elderly psychoses. Quetiapine has traditionally been dosed twice daily. However, a recent study has shown that many patients can be maintained on a single daily dosage given at bedtime to avoid daytime somnolence (77).

Tolerability and Safety. The clinical effectiveness of quetiapine is greatly enhanced by its low propensity to produce EPS or elevation in prolactin. In both side effects, quetiapine's profile is close to placebo (78,79). As with the other atypical antipsychotics, TD is much less common than with conventional antipsychotics. In the head-to-head trial with risperidone, the investigators noted that overall tolerability of the 2 agents was similar but that quetiapine has a better EPS profile (64). In the risperidone group, 12.9% of patients required antiparkinsonian medication for emergent EPS, compared with 3.5% of those in the quetiapine group (Figure 3) (64).

In terms of weight gain, initial increases have been reported using quetiapine, but in a longer-term (18-month) study, quetiapine was shown to be weight neutral (80). Unlike other atypical antipsychotics, the low incidence of EPS, prolactin

elevation, and weight change remains consistent across the dosage range.

Speculation of a possible link between quetiapine treatment and lenticular opacities was first raised when beagles receiving 4 times the recommended human dosage developed cataracts. Even though a causal relation between quetiapine and lens abnormalities has not been established in humans, the manufacturer does recommend regular follow-up eye examinations (55).

Orthostatic hypotension may be a concern in patients with cardiovascular problems, and thus strategies to reduce the risk—such as slower titration to the target dosage or administering the agent at bedtime—can be employed (55).

Quetiapine has been shown to have a low incidence of TD in elderly patients (approximately 2.7% of patients per year), a population that is typically more susceptible to such adverse events (81).

Quetiapine's favourable profile in the tolerability domain makes it an attractive option for switching when unacceptable effects are experienced on other medications, including other atypical antipsychotics. Switching and dosing strategies have been compiled by Cutler and others (82).

Like olanzapine, quetiapine is associated with a fairly high incidence of somnolence. This effect is transient in most patients in 1 to 2 weeks (55), particularly if the target dosage is attained within the first week of therapy. While somnolence may pose a problem for those who need to remain alert during the day, it can also enhance the drug's clinical effectiveness in patients experiencing insomnia and agitation, especially when given at bedtime.

Function. Quetiapine's efficacy in symptom reduction in the above-mentioned patient populations can result in improved quality of life for a broad range of psychiatric patients. In addition, its favourable tolerability make it the atypical least likely to degrade quality of life for most patients with side effects. For some, however, quetiapine-associated somnolence can initially decrease their quality of life.

In terms of cognitive function, quetiapine has demonstrated significant improvements in cognitive function, compared with haloperidol, in 2 studies in schizophrenia (58,83). These studies reported that quetiapine treatment was associated with improvements in verbal reasoning and fluency, immediate recall, executive skills, visuomotor tracking, and overall cognitive scores.

Acceptability. The efficacy and tolerability profiles of quetiapine make it an attractive option in terms of patient acceptability. Patients who feel better on this medication will be more likely to continue to comply with the medication given its relatively benign side effect profile. This may be particularly important in the long-term. In a study of 129 patients who had received quetiapine for at least 6 months (range 6.1 to 47.2 months), over 75% were "very" or "extremely" satisfied with their treatment, and 97% preferred quetiapine to their previous therapy (84).

The number of daily dosages can also affect adherence to treatment. Typically, agents prescribed with fewer daily dosages yield better compliance rates than those with multiple daily dosages. A double-blind crossover trial of once- vs twice-daily quetiapine showed that there were no significant differences in response between once- and twice-daily regimens (73). As is the case with all the atypical agents, it is preferable to concentrate the dosage in the evening. Just as the effective dosage will differ from patient to patient, titration strategies may also differ depending on individual patient profiles. That being said, however, a pilot study in patients with acute schizophrenia showed that there were no significant differences in efficacy or tolerability in regimens titrated to effective dosages (400 mg daily) over 2, 3, or 5 days (85).

Summary. As has been the case with each of the atypical antipsychotics, prescribing quetiapine should be a process that takes into account the various domains of clinical effectiveness. Quetiapine's efficacy has been documented in a number of different settings and its favourable tolerability relative to the other atypical antipsychotics is particularly appealing for acceptability in the long-term.

Conclusion

The atypical antipsychotics are used effectively in many conditions, including schizophrenia, bipolar disorder, and psychoses in older adults. Although older antipsychotics, such as haloperidol, are also considered acceptable first-line treatments, the Canadian guidelines for the treatment of schizophrenia state that the "fewer extrapyramidal side effects (EPS), possible greater decreases in negative and associated symptoms (such as depression and hostility); less adverse impact on cognitive functioning and, in some patients, improved cognition" have made the atypical agents the treatment of choice for many physicians (9).

Efficacy studies have long been the standard in evidence-based medicine. Typically, the focus of these studies has been on the main outcome endpoint, often to the exclusion of such important parameters as safety, tolerability, quality of life, and acceptability. The clinical effectiveness model presented above allows for a consideration of all these parameters, not only from randomized, clinical trials, but also from more "real-life", community-based, and observational studies. Information from all these sources can be divided into the four main domains of clinical effectiveness: efficacy, tolerability and safety, function, and acceptability.

The atypical antipsychotics all have different profiles of clinical effectiveness. For the most part, the agents all have comparable efficacy in the various disorders studied, although clozapine has been shown to be most effective in patients with schizophrenia resistant to other therapies.

In terms of tolerability and safety, there are greater variations between the agents. Clozapine is associated with a minimal,

yet definite, risk of life-threatening blood dyscrasias, which can be safely prevented by regular blood monitoring. Risperidone's tendency to cause EPS and hyperprolactinemia similarly limits its tolerability and acceptability for certain patients. Olanzapine may cause significant dosage-related EPS and weight gain and has also been linked to diabetes mellitus and hypertriglyceridemia. Of the 4 agents, quetiapine's tolerability and safety profile is the most benign.

The third domain, function, is, in part, dictated by efficacy and tolerability. For clozapine, however, the added element of a mandatory blood-monitoring program and possible cardiovascular toxicity can have a significant impact on quality of life for patients taking that drug.

The fourth domain, acceptability, is a large part of clinical effectiveness, with all the other domains contributing to influence a given agent's acceptability. For an intervention to be successful, the regimen must be followed as prescribed. Regimens can be simplified by prescribing the medication at bedtime. Interventions that are more acceptable are more likely to be followed.

Clinical effectiveness is not a model that can be applied with broad strokes to entire patient groups. Each patient being considered for antipsychotic treatment should be evaluated according to his or her own unique profile. Based on the clinician's assessment of that particular patient, the most clinically effective agent can be selected, with the goal of optimizing treatment outcomes.

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