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First-Episode Schizophrenia

A Focus on Pharmacological Treatment and Safety Considerations

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Abstract

Schizophrenia is a debilitating disorder, which is usually chronic, and is one of the most devastating medical illnesses. Early and appropriate treatment with antipsychotics is an important strategy for patients with first-episode schizophrenia. However, there are many possible safety issues for patients with schizophrenia that should be considered and properly addressed.

Depressive symptoms and suicidal behaviour commonly occur in first-episode schizophrenic patients, and every effort should be made to treat and minimise

these symptoms. There are also important issues and considerations in young and first-episode patients that should also be considered in the emergency treatment setting and for minimising medication nonadherence in this population. Most importantly, adverse effects should be considered, minimised and addressed. While first- and second-generation antipsychotics (SGAs) both appear to offer similar efficacy for amelioration of positive symptoms in first-episode patients, SGAs may offer better tolerability, specifically regarding extrapyramidal symptoms (EPS) and tardive dyskinesia risk, and some prolactin-sparing benefits. However, these medications do cause a host of adverse effects, including weight gain, metabolic disturbances, corrected QT interval prolongation and prolactin-related adverse effects, which are important considerations relating to both the short- and long-term safety of patients with schizophrenia being treated with SGAs. Clozapine and olanzapine are most likely to cause weight gain and metabolic effects, while risperidone is more likely to cause EPS and prolactin elevations. Most antipsychotics should be used in low doses to minimise adverse effects and each medication should be optimised in a highly individualised way to maximise adherence and treatment outcomes and minimise tolerability and safety concerns. At some point in their lives, these patients will most probably experience periods of depression, suicidal behaviours, adverse effects and nonadherence, and every effort should be made to minimise or prevent these from occurring. Thus, safety concerns in this group of young patients, in the beginning of their first psychotic episode, are a major issue as they are starting a journey of antipsychotic treatment that is likely to last for the remainder of their lives.

Schizophrenia is a debilitating, usually chronic, disorder and is one of the most devastating medical illnesses. The worldwide lifetime prevalence rate is almost 1% and it is the fourth leading cause of disability among adults.[1] Diagnostic criteria and pharmacotherapy are presently focused on the psychotic pathology of schizophrenia, which involves disorganised thought and behaviour, and reality distortion symptoms such as hallucinations and delusions. This aspect of the illness typically evolves slowly during adolescence and young adulthood in males (slightly later in females). Schizophrenia is a clinical syndrome, probably comprising several disease entities but all associated with psychotic symptoms. Most forms of the disease also involve a range of impairments in cognitive function, and many cases have a deficit syndrome involving avolition, restricted affect and poverty of speech (i.e. primary negative symptoms). The cognitive and negative pathologies account for much of the poor social and functional outcomes observed in schizophrenia. Rates of employment, marriage and independent living are substantially lower than population norms, and about 10% of patients with schizophrenia die by suicide.[2] Whether chronic or episodic, schizophrenia is associated with lifelong problems. Treatment aimed at reduction in symptoms and prevention of relapse is necessarily long term.

The onset of psychosis, whether insidious or acute, is marked with difficulties for patients, families and clinicians. The severity of symptoms may be denied and the medical nature of behavioural disturbance may be misunderstood. The afflicted persons often keep symptoms hidden from family and friends, may remove themselves emotionally and geographically from social support networks, and often confound psychosis onset with substance abuse. The gradual development of psychosis, combined with misunderstanding of symptoms, creates a substantial time window between symptom onset and initiation of diagnosis and treatment. The first

challenge of effective therapy is to move treatment initiation closer to the onset of psychosis.[3]

Antipsychotic drug therapy and selected forms of psychosocial therapy are efficacious for reduction of psychotic symptoms and delay/prevention of psychotic exacerbation/relapse. The short-term prognosis for patients with their first episode is good. For example, Lieberman et al.[4] reported that 74% of their study cohort recovered without residual symptoms and 12% remitted partially. However, many patients have trait impairments in cognitive functions, restricted affect and reduced drive that precede psychosis and persist after symptomatic recovery. In a representative sample of treated first-episode patients, Mojtabai et al.[5] found significant impairment in functional outcomes and symptom status during a 2-year follow-up period. The importance of continuation therapy was illustrated in another recent first-episode study where virtually all patients had a mild symptom exacerbation following gradual medication withdrawal after a prolonged period of stability.[6]

Several issues may confound treatment and should be considered in first-episode patients. Younger patients are more sensitive to drug adverse effects. This is a critical point as patients recently diagnosed and who have fairly good control of symptoms may be much more likely to be affected physically and socially by weight gain and prolactin-related adverse effects. First-episode patients are also more likely to engage in substance abuse, are more likely to have depression and suicidal ideation, and are more nonadherent with antipsychotic treatments.[7-9] Poor adherence is considered to be a key factor associated with relapse. Robinson et al.[10] found that the risk of relapse in patients with early disease was almost five times greater when not taking antipsychotic medications. Furthermore, the time to remission increases in subsequent episodes. Lieberman et al.[11] reported that mean time remission for patients in their first episode was 47 days. Time to remission in the second and third episodes increased to 74.5 and 130 days, respectively. Relapse prevention, patient tolerability and safety are central goals of early treatment.

There is now substantial emphasis on early detection and treatment initiation in first-episode patients.[12,13] It is almost self-evident in medicine that treatment effectiveness is greatest when initiated early in a pathological process. Antipsychotic drug treatment in schizophrenia may be symptomatic therapy rather than altering an underlying pathological process, but clinical prudence supports the early intervention with antipsychotic drugs. An additional and influential hypothesis is that psychosis is 'toxic' in some sense, and that the length of psychosis experience alters the future course of the illness and the individual's responsiveness to treatment. Duration of untreated psychosis (DUP) is associated with poorer treatment response and longer-term outcome;[14] however, the causal effect is not yet established. Not all studies substantiate this effect, suggesting that it may not be robust or ubiquitous. Furthermore, insidious onset is a validated poor prognostic indicator, and an insidious onset is naturally associated with a delay in coming to medical attention. Failure to separate insidious onset from DUP confounds the often-reported association of DUP with poor outcome. Short periods of delay in antipsychotic drug treatment found in placebo-controlled clinical trials and off-medication research studies do not appear to be associated with poor long-term outcomes.[15-19]

This article emphasises safety issues and specific considerations with antipsychotic drug therapy in patients with first-episode schizophrenia as well as discussing other considerations such as suicide and safety issues with acute emergency treatment. The general framework in which safety issues are considered involves the following propositions.

1. It is clinically prudent to detect and treat psychosis as early as possible.

2. Psychosocial treatments are vitally important, but will not be considered here (see Lehman and Steinwachs[20] for a review of evidence-based psychosocial therapies for schizophrenia).

3. Antipsychotic drugs treat psychosis and are therapeutic in first-episode patients even if schizophrenia does not turn out to be the diagnosis at follow-up. First-generation antipsychotics (FGAs) and second-

generation antipsychotics (SGAs) appear to work similarly in this population for the treatment of positive symptoms. However, SGAs are a heterogeneous group of medications and differences may exist in their effectiveness for other symptom domains.

4. Younger patients in their first episode of psychosis are known to have a higher potential for adverse effects. Mainly because of this fact, SGAs are recommended as first-line treatment in this population.[21] Adverse effects from SGA treatment are presented in this article in addition to describing adverse effects that occur more frequently in the young population.

5. The prevalence of depression is high in patients in their first episode of schizophrenia and suicidal behaviour is known to be higher in this group. Therefore, specific considerations for depressive symptoms and suicidal tendencies should be made in this population.

6. Patients experiencing their first psychotic episode may present to emergency settings and may exhibit dangerous or threatening behaviours. Special precautions for safety and specific considerations for acute treatment are warranted.

7. Medication nonadherence is a problem with any long-term treatment; however, it is especially problematic in patients early in their course of schizophrenia. Relapse from nonadherence may be associated with negative consequences, many of which are highly related to the risk of emergency treatment and suicidal behaviours. Thus, medication adherence is highly important for the long-term outcomes and, ultimately, the safety of patients with schizophrenia.

1. Diagnosis and Course of First-Episode Schizophrenia

A person presenting for the first time with psychotic symptoms requires a comprehensive assessment and differential diagnosis as psychosis is not pathognomonic for schizophrenia. Psychosis can be present with a wide array of neurological, psychiatric and general medical conditions. Johnstone et al.[22] found seizure disorder, syphilis, substance abuse, sarcoidosis, lung cancer, thyrotoxicosis and head trauma as the aetiology in about 6% of 268 patients presenting with first-episode psychosis. As patients generally present with a short history of psychopathology and have problems recalling historical information accurately, the most important clinical data for differential diagnosis are often not readily available. Substance abuse, comorbid medical illnesses and psychosocial factors often confound the situation.[3,23] All patients presenting with a first-episode psychosis should have a thorough medical evaluation, including a review of systems and a physical examination that includes a neurological evaluation. According to the American Psychiatric Association Practice Guidelines and the Expert Consensus Guideline Series a person presenting with psychosis should receive laboratory assessments including electrolytes, blood urea nitrogen, creatinine, glucose, liver function profile, thyroid function studies, syphilis serology, serum pregnancy test, urinalysis and urine toxicology. Additionally, an ECG is recommended, particularly in patients with cardiac risk factors or a family history of cardiac conduction defects. Neuroimaging techniques (i.e. brain magnetic resonance imaging or CT scan) do not have sensitivity/specificity to be applied in the diagnosis of schizophrenia. They may be used as a secondary assessment to exclude neurological lesions. This is indicated if neurological signs and symptoms such as asymmetry, weakness or altered sensorium are present.[21,24]

Often the most challenging issue in diagnosing schizophrenia is differentiating it from other psychiatric disorders. Patients presenting with psychotic symptoms for the first time will often exhibit manic or depressive symptoms; thus, differentiating a mood disorder from a psychotic disorder may be problematic. Illicit substance abuse such as lysergic acid diethylamide (LSD), phencyclidine (PCP), cocaine and marijuana can produce psychosis and agitation similar to schizophrenia, and drug use is common in patients within their first episode of illness.[25] However, diagnostic criteria require that the psychotic symptoms persist for at least 1 month to exclude a diagnosis of substance-induced psychotic

disorder.[26] Brief psychosis may also occur, mostly in women and those with borderline or schizotypal personality disorder. These symptoms are usually characterised by florid symptoms, confusion and emotional turmoil in the context of an emotional stressor.[27]

First-episode schizophrenia patients have impairments in many dimensions, including both behavioural and cognitive functioning. Prodromal symptoms may appear before the onset of frank psychosis and patients often do not present immediately in hospitals after the onset of psychosis.[28] Keshavan and Schooler[29] have published a list of six clinical points that are generally considered when diagnosing the onset of first-episode schizophrenia. These point are: (i) decline in social functioning; (ii) onset of general behavioural symptoms; (iii) onset of positive symptoms; (iv) onset of negative symptoms; (v) first treatment; and (vi) first hospital admission. Once schizophrenia is diagnosed appropriate long-term treatment with antipsychotic medications should be initiated.

2. Antipsychotic Treatment Efficacy for First-Episode Schizophrenia

Early detection and intervention in schizophrenia is important for maximising outcomes. Thus, antipsychotic medication should be initiated as soon as psychotic symptoms are recognised. While SGAs are moving quickly into first-line therapy for schizophrenia treatment and are currently recommended for first-episode patients,[21,30] one must keep in mind that FGAs, when used in low doses, are equally effective for initial treatment in first-episode schizophrenia. In the past excessive doses of haloperidol and other FGAs were used leading to high rates of adverse effects and discontinuation from treatment. Much clinical and neuroimaging data suggest no real advantage of dosages of haloperidol exceeding 5 mg/day.[31] In fact, a recent study by Oosthuizen et al.[32] reported that dosages between 1 and 2 mg/day were effective and well tolerated in a 12-week study in first-episode schizophrenia patients. Additionally, many studies comparing SGAs with haloperidol have found no difference in efficacy with the various antipsychotics, especially when haloperidol is used in lower dosages.[33]

The SGAs currently available in the US are clozapine, risperidone, olanzapine, quetiapine and ziprasidone. Aripiprazole is also available, but is often termed a third-generation antipsychotic because it is a partial agonist at the dopamine D_2 receptor (for purposes of this paper it will not be differentiated as a third-generation antipsychotic). Clozapine, while a superior option in treatment-resistant schizophrenia, is not recommended as initial therapy in first-episode patients. In fact, a few recent reports have found no significant advantage of using clozapine as compared with FGAs in first-episode patients. For example, Lieberman et al.[34] found approximately 80% remission within 1 year for both clozapine- and chlorpromazine-treated patients.

However, there is a striking paucity of randomised controlled clinical trials specifically for the treatment of patients in their first episode of schizophrenia. In the younger population, many reports exist for SGAs for many childhood diagnoses such as obsessive-compulsive disorder, pervasive developmental disorders, Tourette's syndrome, conduct disorder and mutidimensionally impaired children and adolescents; however, the results of use in these populations is beyond the scope of this article. It must be kept in mind, however, that using these medications for other diagnoses or target symptoms still carries the same safety and adverse effect considerations, as does the use of these medications for new-onset psychosis. Sections 2.1 to 2.5 provide a brief summary of the pharmacology of the available SGAs in the US (excluding clozapine) and published efficacy data specifically for patients in their initial episode of psychosis.

2.1 Risperidone

Risperidone, a benzisoxazole derivative, was the first medication to be marketed as a first-line SGA following the release of clozapine. This antipsychotic has high binding affinity to both serotonin 5-HT_{2A} and D_2 receptors, and binds to α_1- and

α_2-adrenergic receptors with very little blockade of cholinergic receptors.[35]

An international, multicentre, double-blind study was conducted in 183 patients between the ages of 15 and 45 years who were diagnosed with provisional schizophreniform disorder or schizophrenia and had no prior treatment with antipsychotic medications. Sixty-three percent of the 99 risperidone-treated patients were clinically improved compared with 56% of the 84 haloperidol-treated group in this 6-week study. Although the symptom changes were significantly different, the risperidone group had fewer withdrawals due to adverse effects, a smaller number of total adverse effects and fewer extrapyramidal symptoms (EPS). In this study, dosages <6 mg/day were the most efficacious and tolerable.[36] Another recent study in adolescents between the ages of 15.5 and 20 years reported significant improvements in positive symptoms in 28% of patients with first-episode schizophrenia when treated with a mean dose of risperidone 3.1mg.[37] Others have also reported that dosages of 2–4 mg/day are more effective than dosages of 5–8 mg/day of risperidone in first-episode schizophrenia.[38] Longer-term outcomes (minimum 1 year) in first-episode patients demonstrate lower lengths of first hospitalisation, overall utilisation of inpatient beds during the course of treatment and less use of anticholinergic medications with risperidone than with haloperidol.[39] A consensus panel of 50 experts recently rated risperidone as the top choice in first-episode schizophrenia patients, most likely because it has the highest volume of efficacy and safety data available.[30]

2.2 Olanzapine

Olanzapine has greater affinity for 5-HT_{2A} receptors than for D_2 receptors. In addition, the compound has affinity at the binding sites of D_4, D_3, 5-HT_3, 5-HT_6, α_1-adrenergic, muscarinic $M_{1–5}$ and histamine H_1 receptors.[40]

Patients with schizophrenia who were included in the pivotal trials for the approval of olanzapine and were characterised as being having first-episode schizophrenia were analysed as a subpopulation of a large international double-blind trial of olanzapine (n = 59) versus haloperidol (n = 24).[41] At endpoint, olanzapine was statistically superior to haloperidol in the reduction of Brief Psychiatric Rating Scale (BPRS) scores, was considerably better tolerated than haloperidol, and significantly more patients continued the trial on this medication, which is likely to be a result of improved tolerability and less dysphoria.[41] It is noteworthy that even though these patients were in the initial episode of schizophrenia they had already been treated for a considerable period and may not be as comparable as a population in the acute early phase of their illness. In another naturalistic open-label study, olanzapine was significantly more effective than FGAs in lowering the total BPRS and Clinical Global Impression (CGI) scores. There were significantly fewer adverse effects, especially EPS, with olanzapine than with FGAs.[42] In a recently published double-blind study of olanzapine versus lower-dose haloperidol in first-episode schizophrenia (n = 263) patients responded similarly to treatment in the 12-week study, with more patients in the olanzapine group completing the trial than those in the haloperidol group.[33]

2.3 Quetiapine

Structurally, quetiapine is related to clozapine and olanzapine. Quetiapine has a high affinity for 5-HT_{2A} receptors and lower affinity for D_2 and D_1 receptors. This drug has some affinity for α_1-, α_2-adrenergic and H_1 receptors, and very little for muscarinic receptors. Only open-label trials have been published regarding the efficacy of quetiapine in first-episode schizophrenia. In a small study (n = 14), 71% of patients were considered 'much improved' or greater on the CGI-Improvement Scale.[43] In an adolescent population with psychotic symptoms, significant decreases in symptoms were observed with quetiapine at both 200 and 800 mg/day, with little evidence of adverse effects.[44] In a recent interim analysis of a 2-year open-label study examining the cognitive effects of quetiapine in first-episode schizophrenia, statistically significant improvements were noted on measures of attention,

verbal productivity and executive function after 6 and 12 months of treatment.[45]

2.4 Ziprasidone

Ziprasidone was developed within a structure-activity investigation intended to find a compound that potently blocks D_2 receptors but binds with even greater affinity to central 5-HT_{2A} receptors. As a result, ziprasidone has a binding affinity ratio of 11 : 1 for 5-HT_{2A}/D_2 receptors. Ziprasidone also binds with relatively high affinity with 5-HT_{2C}, 5-HT_{1D}, α_1-adrenergic and D_1 receptors.[46] To date, there are no published studies or reports of ziprasidone treatment for psychotic symptoms in adolescent or first-episode schizophrenia.

2.5 Aripiprazole

Aripiprazole was discovered in the early 1980s in an attempt to find an antipsychotic that would function as a potential entity with both antagonist and agonist activity to the D_2 receptor. *In vitro* data suggested that the dopamine autoreceptor agonists were effective in treating negative symptoms of schizophrenia.[47] Potent dopamine postsynaptic receptor antagonism was believed to be necessary for positive symptoms of schizophrenia. Hence, aripiprazole is the first potent partial D_2-receptor agonist for the treatment of schizophrenia (third-generation antipsychotic). In a hyperdopaminergic state, aripiprazole functions as an antagonist, while under conditions of hypodopaminergic activity it functions more like an agonist. This novel mechanism has seen aripiprazole labeled as a dopamine system stabiliser. Aripiprazole also has high affinity for D_3 receptors. It is a partial agonist at 5-HT_{1A} receptors and an antagonist at $5HT_{2A}$ receptors. Aripiprazole has a moderate affinity for α_1-adrenergic and H_1 receptors, with no appreciable affinity for the M_1 receptor.[48] As yet, no published reports in first-episode schizophrenia are available; however, trials are under way.

3. Safety Considerations with Antipsychotic Treatment

Selection for use among antipsychotics in first-episode schizophrenia is largely determined by the adverse effect profiles of the medications. Among the classes of antipsychotics, adverse effects are highly variable. Between 25% and 66% of patients who are nonadherent to prescribed antipsychotic therapy cite adverse effects as the primary reason for noncompliance. EPS, most notably akathisia, sexual dysfunction and weight gain are the three most cited adverse effects associated with nonadherence.[49] As discussed further, patients with first-episode schizophrenia may be at higher risk for some adverse effects and rates of nonadherence may be higher in this population.

If FGAs are selected in this population, the key to effective therapy is using low doses (haloperidol <5 mg/day).[32] These medications are associated with high rates of nonadherence and rates of dysphoria, EPS and tardive dyskinesia are highest among the antipsychotic medications. The SGAs have real advantages relating to the production of EPS, but the overall safety of these drugs is now coming under close scrutiny. As a result of the expanded use of the SGAs, much literature regarding weight gain and related consequences during treatment has emerged. The long-term consequences of weight gain have the potential to surpass the problems of EPS and tardive dyskinesia if these problems are not studied and addressed. Metabolic disturbances associated with antipsychotic treatment may lead to morbidities such as cardiovascular disease, cancer, osteoarthritis, type 2 diabetes mellitus and early death.[50] Other issues may affect adherence and safety, such as prolactin-related effects and changes in the corrected QT (QTc) interval.

Treatment aims are to weigh the risk-benefit profile for each antipsychotic and to match patients with individual risks of these medications. Safety issues and considerations with antipsychotics are similar for both first-episode and multi-episode patients treated with these drugs, and little safety data are available pertaining particularly to the first-episode patients. Nonetheless, the younger population

is at particular risk for some adverse effects and these are discussed further. In this section, specific attention is paid to the safety of antipsychotics with regards to EPS and tardive dyskinesia, weight gain, glucose dysregulation, lipid changes, prolactin-related adverse effects and effects on the QTc interval. Additionally, each antipsychotic is evaluated for commonly occurring or unique adverse effects not mentioned earlier.

3.1 Extrapyramidal Symptoms and Tardive Dyskinesia

EPS, including akathisia, dystonia and pseudoparkinsonism, are the major adverse effects associated with FGA therapy. These adverse effects are a result of dopamine antagonism in the nigrostriatal pathways. Akathisia is the most frequently occurring of these adverse effects; approximately 20–40% of patients treated with FGA drugs will experience a subjective feeling of restlessness.[51] The onset of akathisia is usually 5–10 days after the first dose or increase in dosage. Younger patients and those taking high doses of high potency antipsychotics are at greater risk for the development of akathisia. Acute dystonic reactions are abrupt in onset and are usually seen within 24–96 hours after a first dose or increase in dosage. Characteristic signs and symptoms include abnormal positioning or spasm of the muscles of the head, neck, limbs or trunk, and may occur in 10–20% of patients. Pseudoparkinsonism resembles idiopathic Parkinson's disease and features may be present in up to 30–60% of patients treated with FGAs. The onset of symptoms is usually seen within 1–2 weeks following initiation or a dose increase. Risk factors include older age, female sex, high doses and, possibly, patients with depressive symptoms.[52-54]

Clinically, the rates of EPS are comparable with the *in vitro* binding of antipsychotics to the D_2 receptors. In clinical trials of multi-episode patients, quetiapine has been found to have no greater incidence of EPS than placebo across all the dose ranges. Aripiprazole, ziprasidone and olanzapine do cause some EPS, and risperidone has the greatest potential to cause movement disorders and does so in a dose-related fashion.[55] The risk of EPS is known to occur at higher rates in first-episode versus multi-episode patients.[56] Aguilar et al.[57] reported that, when treated with haloperidol 15 mg/day, 60% of drug-naive patients developed acute dystonia. Emsley et al.[36] found rates of antiparkinsonian medication use to be 75% with haloperidol and 50% with risperidone in a first-episode patient treated with a mean risperidone dose of 6.1 mg/day. In the lower dosage group (<6 mg/day) the rates of anticholinergic use with risperidone remained high (46%). Another study comparing long-term outcomes of FGAs with risperidone (mean dosage 2.5 mg/day) reported rates of anticholinergic medication use of 84% with FGAs and 21% with risperidone.[39] A study designed to measure EPS in first-episode patients found rates of akathisia or parkinsonian adverse effects to occur in 32% of patients receiving dosages of risperidone between 5 and 8 mg/day. Those treated with dosages between 2 and 4 mg/day did not experience EPS at this range.[38] It is clear that rates of EPS occur more frequently regardless of FGA or SGA treatment in younger patients compared with reported rates (discussed earlier) in multi-episode or chronic schizophrenia patients. Thus, this population should be treated with the lowest possible dose, particularly with risperidone, a medication that binds strongly to D_2 receptors.

Tardive dyskinesia is a movement disorder characterised by abnormal choreiform (rapid, objectively, purposeless, irregular and spontaneous) and athetoid (slow and irregular) movements occurring late in relation to initiation of antipsychotic therapy. This adverse effect usually develops over several months and occurs after at least 3 months of antipsychotic treatment. The estimated average prevalence is 20% with a range of 13–36%. The incidence of new cases per treatment year with FGAs is approximately 5%.[58] Rates of tardive dyskinesia in first-episode patients followed up for up to 8.5 years were found to be 6.3% at 1 year, 11.5% at 2 years, 13.7% at 3 years and 17.5% at 4 years when treated with FGAs.[59] However, a recent study using low-dosage haloperidol (mean 1.7 mg/day) reported a 12% inci-

dence at 1 year.[60] Tardive dyskinesia is reversible with the cessation of the antipsychotic in one-third to one-half of patients. When the antipsychotic is tapered or discontinued there is usually an initial worsening of abnormal movements. Risk factors include older age, duration of antipsychotic treatment, and higher rates of EPS, substance abuse and mood disorders. Total drug dose was found to be a predictor of time to tardive dyskinesia incidence in patients in their first episode of schizophrenia.[59]

The characteristic signs and symptoms of tardive dyskinesia usually involve bucco-lingual-masticatory syndrome or orofacial movements. Typically, these are the first detectable signs of tardive dyskinesia and can progress to movements severe enough to interfere with chewing, speech, respiration or swallowing. These include lip smacking, puckering, sucking, pouting, tongue writhing, protrusion and tremor. Other facial movements include frequent blinking, grimacing and tics.

Tardive dyskinesia with all the SGAs appears to occur at an incidence of <2%, but few long-term follow-up studies are available and comparator doses of conventional antipsychotics have been high.[61] Olanzapine, risperidone and quetiapine have all been implicated in a few case reports to both treat pre-existing tardive dyskinesia and causing this adverse effect.[62] However, the incidence with all of the SGAs appears to be minimal and much lower than the risk associated with FGAs. Beasley et al.[63] published a double-blind comparison of olanzapine and haloperidol in over 1600 subjects and evaluated tardive dyskinesia for up to 2.6 years. The relative risk of tardive dyskinesia over 1 year was 7.5% with haloperidol and 0.5% with olanzapine. In two long-term studies of risperidone in elderly adults the risk of newly developing tardive dyskinesia was <1%.[64,65] Long-term studies are not available for quetiapine, ziprasidone or aripiprazole; however, the risk appears to be low with all the newer antipsychotics.

3.2 Weight Gain

One-half of adults in the US are currently overweight (body mass index [BMI] >25 kg/m^2) and one-fifth of the population is considered to be obese (BMI >30 kg/m^2).[66] However, BMI among patients with schizophrenia exceeds the general population estimates.[67] Many patients with psychiatric disorders, including those with schizophrenia, have sedentary lifestyles with little exercise as well as potentially already being predisposed to metabolic effects associated with weight gain. In a recent study in first-episode drug-naive patients, higher levels of visceral fat stores were present in those with schizophrenia compared with normal controls.[68] Obesity, in general, increases the risk for a myriad of medical disorders such as hypertension, stroke, cancer, diabetes and atherosclerosis.[50] Patients with schizophrenia exhibit high relative rates of smoking and drug abuse and have several medical disorders that also compound the high rates of morbidity and mortality seen in this population.[69]

Many short-term studies describe weight gain among patients taking various antipsychotic drugs. The most comprehensive report to date is a meta-analysis of over 80 studies. Weight gain is highly variable among antipsychotics. Haloperidol is associated with modest weight gains of about 1–2kg over 10 weeks, while lower potency agents are associated with higher gains (3–5kg over 10 weeks). Two SGAs, olanzapine and clozapine, clearly appear to be associated with the highest degree of weight gain among all antipsychotics in short-term trials (4–4.5kg over 10 weeks).[70] Additionally, the percentage of patients with a >7% increase in bodyweight from baseline in pivotal SGA trials is shown in table I.

Significant weight gain is widely known to occur with olanzapine treatment. Olanzapine weight gains at dosages of 12.5–17.5 mg/day have been found to

Table I. Percentage of patients with a >7% increase in bodyweight from baseline with atypical antipsychotic treatment[70-72]

Drug	Increase with drug (%)	Increase with placebo (%)
Aripiprazole	7	1
Ziprasidone	10	4
Risperidone	18	9
Quetiapine	25	4
Olanzapine	29	3

average 12kg after 1 year of use.[73] Kinon et al.[74] reported mean weight gains of 6.3kg after 1.05 years. This number is most likely to be conservative as it was reported in an intent-to-treat design. Weight gain with olanzapine appears to peak after 40 weeks of treatment and may be greater than gains associated with clozapine treatment.[75] Weight gain with risperidone appears to plateau early on and remain at about 2–3kg at 1 year. A long-term flexible-dose comparative study of risperidone and haloperidol reported a mean increase in weight of 2.3kg in risperidone-treated subjects, which was significantly greater than haloperidol over 52 weeks.[76] Studies on long-term quetiapine treatment have reported maximum weight gains of approximately 1–2kg over at least 1 year.[77,78] Ziprasidone is associated with no or minimal (≤1kg) weight gain in subjects followed up for up to 1 year.[79,80] Aripiprazole is associated with approximately 1kg weight gain in subjects treated for 6–12 months.[81] Most data imply that weight gain is generally not dose dependent with the SGAs and that patients with low BMIs may gain the most weight.

While it is known that weight gain occurs fairly frequently in patients treated with SGAs, first-episode and younger patients are even more likely to experience weight gains. In a 6-week trial of olanzapine versus haloperidol, patients with first-episode schizophrenia gained 4.1kg versus 0.5kg on haloperidol.[41] Another study addressing weight gain in first-episode patients receiving olanzapine plus placebo or olanzapine plus fluoxetine for 8 weeks reported 8kg gains in the patients in the latter group.[82] Patients in olanzapine plus placebo group gained 6kg. Over 60% of the patients in either group gained at least 7% of their initial weight. In a comparative study of olanzapine versus risperidone average weight gains during 12 weeks were 7.2kg and 3.9kg, respectively. Extreme weight gain (>7%) was reported in 91% of the total group.[83] Other studies have also reported high gains in weight in patients receiving risperidone. Gains of 7.0kg have been reported over 5 months[84] and 8.6kg over 6 months with risperidone.[85] Weight gain has been reported to be 4.1kg during 8 weeks of quetiapine treatment in adolescents who were psychotic.[86] All these studies demonstrate significantly higher weight gains in younger patients than seen in studies with older or first-episode patients.

3.3 Glucose Dysregulation

Metabolic disturbances, particularly impaired glucose metabolism, were first described in psychotic patients prior to the introduction of antipsychotic medications. The risk for diabetes is also known to be higher in individuals with schizophrenia than in the general population.[67] A recent study reported that drug-naive first-episode patients with schizophrenia had significantly higher fasting plasma levels of glucose and insulin than healthy controls. This study also reported more insulin resistance in patients with schizophrenia.[87] In addition, antipsychotic medications are associated with impaired glucose metabolism, exacerbation of existing type 1 and 2 diabetes, new-onset type diabetes and diabetic ketoacidosis. Possible consequences of diabetes include retinopathy, cataracts, infection, neuropathy, kidney failure and circulatory disorders. Abdominal or central adiposity may contribute to glucose dysregulation.[88] However, diabetes may occur with olanzapine independent of weight change.

A recent population-based nested case-control study of approximately 20 000 schizophrenia patients found those receiving olanzapine to have a significantly increased risk of developing diabetes than those taking FGAs (odds ratio [OR] 4.2). Risperidone treatment was found to have a slightly elevated but nonsignificant risk compared with FGA treatment (OR 1.6).[89] Koller and Doraiswamy[90] recently published epidemiological reports detailing both spontaneously reported cases of diabetes that have been reported to the US FDA's MedWatch Drug Surveillance System and published case reports through to May 2001. There were 237 cases of diabetes reported for olanzapine, with diabetic ketoacidosis occurring in 80 patients and death in 15 patients. Improvements in glycaemic control were evident in most patients once the drug was discontinued. Men and African Americans may be at a higher risk for the development of diabetes, and

weight gain is not prominent in up to 50% of patients developing diabetes.[91]

Of all the first-line SGAs, olanzapine treatment has been associated with the highest rates of diabetes.[92] Many studies and case reports exist for olanzapine while only a few case reports exist for risperidone, quetiapine, ziprasidone and none thus far for aripiprazole.[93-100] In young patients (aged 13–18 years), nine cases of diabetes occurring with olanzapine between 1996 and 2001 were reported to the US FDA Drug Surveillance System.[101]

3.4 Hyperlipidaemia

Increases in plasma lipid levels have been noted with the phenothiazines, but negligible effects on lipids have occurred with the higher potency drugs such as haloperidol. A report by Sheitman et al.[102] suggested that olanzapine treatment might result in marked increases in triglyceride levels for some individuals. Another cohort study of 25 inpatients treated with olanzapine for 12 weeks showed a mean increase of 60 mg/dL in fasting triglyceride levels.[103] Others have also reported significant increases in triglycerides during longer term treatment.[98,104] In a recent study using the UK-based General Practice Research Database, the prescription of olanzapine was associated with a statistically significant 4-fold increase in the odds of developing hyperlipidaemias compared with those not prescribed antipsychotics (OR 4.65, $p < 0.001$). No significant increase was noted for risperidone in the sample of approximately 20 000 individuals.[105] In a recent 1-year study, triglyceride levels significantly increased by 104.8 mg/dL in patients treated with olanzapine, while small increases (31.7 mg/dL) were noted for risperidone.[106] A few cases of high triglyceride levels have been reported with quetiapine.[104] Risperidone, ziprasidone and aripiprazole appear to have neutral effects on triglyceride and total cholesterol levels; however, long-term studies on lipid changes are lacking.[107] Studies are also needed for lipid changes in first-episode or young patients.

3.5 Prolactin-Related Adverse Effects/ Sexual Dysfunction

While there may be many contributing factors leading to sexual dysfunction, the evidence for elevated prolactin levels contributing to sexual dysfunction is convincing.[108-112] As early as 1968, literature began to emerge pertaining to sexual dysfunction from FGA treatment.[113] While the 'normal sexual functioning' of patients with schizophrenia remains largely unknown, it is known that approximately 50% of patients have reported dysfunction in the area of sexuality during treatment with FGAs.[114,115] More recent reports have reported rates as high as 80–90% with both sexes.[116] The SGAs as a class vary in their propensity to cause prolactin elevations and very little long-term data are available. Direct correlations between prolactin levels and sexual dysfunction have not been firmly established; however, rating instruments have not been systematically used. In addition to sexual disturbances, other potential long-term consequences of elevated prolactin may include an increased risk for osteoporosis and breast cancer; however, more research is needed in this area.[117-119]

Of all the SGAs, risperidone has the highest propensity to elevate plasma prolactin levels and does so in a dose-related fashion.[120] Mean prolactin levels at doses of 3mg are about 27 ng/mL, which is significantly higher than olanzapine or clozapine.[121] Studies actively questioning patients have produced fairly high rates of prolactin-related effects; menstrual changes were reported to occur in 24% of patients treated with risperidone compared with 20% with olanzapine.[122] A recent retrospective chart review reported a significantly higher proportion of sexual dysfunction with risperidone compared with haloperidol and clozapine.[123] Other prospective, comparative studies have found higher rates of both sexual dysfunction and reproductive adverse effects with risperidone compared with olanzapine, quetiapine and haloperidol.[124] Additionally, several case reports in the literature describe sexual dysfunction during risperidone treatment. For males, reports describe gynaecomastia,[125-127] galactorrhoea,[126] priapism[128,129] and

ejaculatory difficulties[125,130] occurring with risperidone treatment. For women, menstrual irregularities are the most commonly reported adverse effect and have occurred at dosages as low as 1 mg/day. Amenorrhoea and galactorrhoea are also reported to occur with fairly low doses of risperidone.[131,132]

Olanzapine causes transient elevations in plasma prolactin levels. In adults prolactin levels remain slightly elevated in about one-third of patients during treatment.[133] Elevation of prolactin appears to be a dose-related phenomenon.[134] Mean prolactin levels during treatment with olanzapine 10–30 mg/day are approximately 17 ng/mL, which is higher than that of normal, drug-free patients and clozapine-treated patients.[135] This same study found levels with haloperidol to be about twice the level with olanzapine. Possibly because of its lower propensity to elevate prolactin, few case reports have been published with regards to sexual dysfunction and menstrual changes. Rates of sexual function in studies actively questioning patients have been reported to be between 30% and 35%.[122,124] At least seven case reports have discussed cases of priapism occurring with olanzapine treatment that may be due to the α-adrenergic- and muscarinic-receptor blockade of this medication.[136]

Quetiapine has negligible effects on the elevation of prolactin. In all of the large trials of quetiapine, prolactin levels were reported to decrease from baseline to endpoint during quetiapine treatment and no differences were noted between quetiapine and placebo.[137-140] In more than 2000 patients treated with quetiapine, menstrual changes occurred in <1% of patients treated.[141] One case of priapism after a quetiapine overdose has been reported and was postulated to be secondary to α_1-adrenergic receptor antagonism.[142] Impotence, abnormal ejaculation and amenorrhoea were reported in pivotal trials to occur in <0.1% of patients.[71] Quetiapine in a recent comparative trial had the lowest risk of sexual dysfunction (18%) compared with rates of 35–43% in patients on risperidone, olanzapine and haloperidol. Of these medications, quetiapine may also have the lowest propensity for reproductive adverse effects (<3%).[124]

Very little data are available pertaining to either plasma prolactin levels or sexual functioning with ziprasidone. It appears that slight elevations may occur with ziprasidone. In a double-blind study prolactin levels were approximately 19 and 60 ng/mL for ziprasidone and risperidone treatment, respectively, at the end of 52 weeks.[143] Impotence, abnormal ejaculation, amenorrhoea, galactorrhoea and anorgasmia occurred in premarketing studies infrequently (<0.1%). One case of priapism in premarketing trials was reported,[71] and only a few case reports have been reported in the literature.[144,145]

Serum prolactin levels during treatment trials with aripiprazole have been found to decrease from baseline across all dose ranges. Levels decreased by about 7 ng/mL during short-term trials[146] and are similar to the decrease with placebo (<15 ng/mL). This remains fairly consistent across longer-term trials.[56,147] The lack of increased prolactin levels may be explained by the partial agonism of aripiprazole at D_2 receptors, in contrast with the D_2 receptor antagonism of other SGAs. Sexual dysfunction was infrequently reported in clinical trials, as noted in product labeling. More studies are needed to specifically address prolactin and sexual dysfunction with aripiprazole.

A few studies are available that describe prolactin changes in young patients on SGAs. Wudarsky et al.[148] reported that mean prolactin levels after 6 weeks of olanzapine remained significantly elevated compared with baseline. In 70% of the olanzapine-treated patients prolactin levels were increased above the upper limit of normal. In contrast, adult data generally describes prolactin levels that return to the normal range during olanzapine treatment. Risperidone has been associated with cases of galactorrhoea in male adolescents[149] and prolactin levels are elevated above normal levels in about 75% of young patients on risperidone.[150] Quetiapine does not appear to elevate prolactin in young patients[86] and data are lacking in this population for ziprasidone and aripiprazole.

In addition to sexual dysfunction, high levels of prolactin may lead to bone loss and a potentially higher risk for osteoporosis. Studies in women with

hyperprolactinaemia resulting from pituitary tumours have demonstrated high rates of osteoporosis believed to result from hypoestrogenism. Similarly, hyperprolactinaemia in men has resulted in bone loss.[117,151] A recent study found that bone mineral density is lower for patients treated with risperidone than in those treated with olanzapine.[152] Long-term effects of conventional antipsychotics and prolactin-elevating agents such as risperidone have not been studied with regards to osteoporosis risk. Additionally, the risk of breast cancer development from dopamine receptor antagonists is starting to gather much attention.[117] Animal studies have raised the possibility that breast cancer may be promoted from prolactin-elevating drugs;[153] however, to date, studies in humans have been limited. A retrospective cohort study compared 52 819 women exposed to dopamine receptor antagonists with 55 289 women not exposed during the same time period. This epidemiological study found a 16% increase in the risk of breast cancer in those treated with dopamine receptor antagonists.[154] Prolactin has been found to act at the endocrine and autocrine/paracrine levels, and functions to stimulate the growth and motility of human breast cancer cells.[155] Interestingly, patients with Parkinson's disease who have used dopamine receptor agonists were found to have a significantly lower rate of breast cancer in a population of 144 364 patients with Parkinson's disease.[156] Despite this emerging focus and the data on osteoporosis risk and breast cancer risk, much more research is needed in this area.

3.6 Effects on the Corrected QT Interval

Psychotropic agents can cause a wide variety of effects that impact on the cardiovascular system. Torsades de pointes is among the most serious cardiac complications that have been associated with psychotropic medication use. This potentially fatal polymorphic ventricular arrhythmia may occur in patients who have a lengthening of the QTc interval.

The QT interval is the period extending from the beginning of depolarisation (QRS complex) to the end of repolarisation (T wave) of the ventricles. The QT interval is shorter with faster heart rates and longer with slower heart rates. Therefore, a correction for rate (the QTc) is applied to make the reporting of the interval more meaningful. QTc intervals are generally considered to be prolonged if they are >450 msec in men or >470 msec in women. In either sex, QTc prolongation >500 msec may place a patient at higher risk for torsades de pointes.[157,158] Recently, the effects of antipsychotic drugs on the QTc interval has received great attention. In a large study, Reilly et al.[159] reported that droperidol and thioridazine were the most likely to cause QTc interval prolongation out of 20 classes of psychotropic medications studied. Furthermore, torsades de pointes has been reported to occur in patients receiving most of the FGA medications.

Several of the SGAs were compared with haloperidol and thioridazine for QTc interval changes in a study presented to the US FDA prior to the approval of ziprasidone.[160] The mean change at steady state in the QTc interval for thioridazine, using Bazett's correction, was the most significant (35.6 msec). Ziprasidone prolonged the interval by an average of 20.3 msec, quetiapine by 14.5 msec, risperidone by 11.6 msec and olanzapine by 6.8 msec. Those treated with haloperidol had a mean increase of 4.7 msec at steady state. Very little long-term safety data assessing QTc interval changes are currently available; however, the risk of sudden death and torsades de pointes is extremely low. One case of sudden death has been reported for risperidone[161] and significant QTc interval prolongations have been reported rarely for quetiapine, ziprasidone and olanzapine, and are generally in high- or overdose situations.[97,162-165] Of all the SGAs, ziprasidone is associated with the greatest prolongation in the QTc interval and it is recommended not to coadminister this medication with other agents that may prolong the QTc interval such as quinidine, pimozide, sotalol, thioridazine, moxifloxacin and sparfloxacin.

Other considerations for using drugs that may prolong the QTc interval include metabolic abnormalities (hypokalaemia, hypomagnesia, hypothyroidism, hypocalcaemia), female sex, hypergly-

caemia, alcoholism, bradycardia and cardiac disease (myocarditis, heart failure, myocardial ischaemia or infarction, rheumatic fever or mitral valve prolapse).[166] Further considerations are low-energy diets, consumption of a large meal, obesity, Parkinson's disease, liver disease or renal insufficiency.[166-168] Patients with diabetes may be at an additional risk as QTc intervals appear to be significantly associated with fasting glucose levels.[166] In fact, even acute hyperglycaemia in healthy adults can produce significant increases in the QTc interval.[169] Despite the higher propensity to prolong the QTc interval, ziprasidone has not yet been linked to cases of torsades de pointes and has only been rarely reported to be associated with elevations in the QTc interval in excess of 500 msec.[71] Data are currently unavailable for QTc interval changes associated with antipsychotic treatment in first-episode patients. While this adverse effect is generally not a major concern in medically healthy patients, specific attention should be paid when selecting antipsychotics in patients with eating disorders, and in those who are malnourished, underweight and have a family history of cardiac disease.

3.7 Antipsychotic-Specific Adverse Effects

3.7.1 Risperidone

The most common spontaneously reported adverse effects for risperidone include insomnia (26%) and agitation (22%). Rhinitis occurs in 10% and gastrointestinal complaints such as vomiting, dyspepsia, nausea, constipation and abdominal pain are reported to occur in about 4–7% of patients. Because of the α_1-adrenergic receptor antagonism of risperidone, orthostatic hypotension may occur which may be associated with dizziness, tachycardia and, rarely, syncope (in approximately 0.2% of patients). Tachycardia has been reported to occur in approximately 3% of patients taking risperidone. Orthostatic hypotension is generally seen during the initial dose titration and is usually transient.[71,170] While sedation is not reported at high rates in older or multi-episode patients, sedation may occur in >30% of first-episode patients.[171]

3.7.2 Olanzapine

Somnolence (26%) and agitation (23%) are the most frequently reported adverse effects with olanzapine in clinical trials. Insomnia occurs in about 20% of patients. Anticholinergic effects such as constipation, dry mouth and tachycardia occur in 7–9%, but may be more frequent at higher doses. Hypotension is reported to occur in 5–7% of those taking olanzapine and tachycardia occurs in approximately 4%. Syncope was reported to occur in 0.6% of olanzapine-treated patients in phase II and III studies. The risk of orthostatic hypotension usually occurs within the initial dose administration period and may be minimised by initiating therapy with a 5mg daily dosage.[71] A more gradual titration to the target dose should be considered if hypotension occurs.

In placebo-controlled studies, clinically significant serum ALT elevations of ≥3 times the upper limit of the normal reference range were observed in 2% of patients taking olanzapine. During premarketing studies the incidences of ALT elevations were also 2%, but were not associated with jaundice or other symptoms attributable to liver impairment. Transient increases may be seen but usually normalise with olanzapine discontinuation.[71,172]

In a large trial separating adverse effect rates in first-episode patients from those in multi-episode patients, asthenia was the only treatment-emergent adverse effect with a frequency of ≥10% that occurred significantly more frequently in first-episode patients.[41] The US FDA's postmarketing surveillance database of spontaneously occurring adverse events was queried by Woods et al.[173] for differential rates of reported adverse effects between adults and adolescents taking olanzapine. Younger patients had higher reported rates of sedation, weight gain, liver function abnormalities and prolactin increases.

3.7.3 Quetiapine

Somnolence is one of the most commonly occurring adverse effects associated with quetiapine treatment (18%) and is usually transient after the first week. Anticholinergic effects occur in <10% of patients and dizziness is reported spontaneously in trials at around 10%.[137] In clinical trials a dose-

related decrease of total and free thyroxine (T_4) of approximately 20% was seen in a few patients in the first 2–4 weeks of treatment and maintained during long-term therapy. This increase was considered not clinically significant. Approximately 0.4% (10 of 2386) of patients experience thyroid-stimulating hormone increases.[71] Quetiapine may also cause orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope. Syncope may occur in approximately 1% of those treated and usually occurs during the initial dose-titration period.[71] Limiting the initial dose to 25mg twice daily may minimise the risk of syncope and hypotension. In first-episode patients, rates of postural tachycardia were reported in 90% and insomnia occurred in 50%, both rates appearing to occur more frequently than in multi-episode or older patients.[42] Additionally, >25% of patients experienced fatigue and sedation.

Asymptomatic transient and reversible elevations in plasma transaminases (primarily ALT) have been reported. Six percent of patients treated with quetiapine in clinical trials were found to have elevations of ≥3 times the upper limit of normal. Hepatic enzyme elevations generally occurred within the first 3 weeks of drug treatment and returned to pretreatment levels after discontinuation of quetiapine.[71] Lastly, the warning for cataract development appears in bold ink on manufacturer labeling, as required by the US FDA. The warning states that the development of cataracts was observed in long-term dog studies and that examination of the lens by slit lamp or other appropriately sensitive methods to detect cataract formation is recommended at initiation of treatment and, thereafter, at 6-month intervals. There have been lens changes occurring in humans after long-term therapy, but a causal relationship has not been established. To date, there are no human reports of cataract formation during quetiapine therapy.[174]

3.7.4 Ziprasidone

Somnolence has been reported to occur in clinical trials in approximately 14% of patients taking ziprasidone, twice that seen with placebo. Gastrointestinal complaints such as nausea, diarrhoea, dyspepsia and constipation are reported in approximately 5–10% of patients. Syncope and orthostatic hypotension occur infrequently and usually during the initial dose-titration period. Seizures occurred in 0.4% of those treated with ziprasidone during clinical trials.[175]

3.7.5 Aripiprazole

Insomnia occurs frequently, with a rate of about 24% in spontaneous reports. However, this adverse effect is reported to be transient and diminishes within the first week.[71] Gastrointestinal complaints also occur initially with nausea and vomiting reported to occur in 12–14% of patients. Sedation is the only adverse effect noted possibly to have a dose relationship occurring most prominently with the 30 mg/day dosage (10–15%).[176] Other adverse effects in clinical trials were not significantly greater than placebo.

3.7.6 First-Generation Antipsychotics

Lower-potency agents (chlorpromazine, thioridazine, mesoridazine) are associated with high rates of sedation, anticholinergic adverse effects and orthostatic hypotension. The phenothiazines are also associated with photosensitivity reactions and patients are advised to wear protective clothing and sunblock when in direct sunlight. Other dermatological adverse effects such as a blue-grey skin discolouration may occur with chlorpromazine treatment.[177]

3.8 Summary of Second-Generation Antipsychotics

In summary, all five SGAs described (excluding clozapine) have been shown to be effective in multi-episode patients, yet the majority of the data support the use of risperidone, olanzapine and quetiapine for first-episode patients, most probably because of the longer market penetrance. Case report data with quetiapine in first-episode patients have shown improvements in cognition that would be important in this group of young, higher functioning patients who are attempting to reintegrate into schools, work and social situations. Risperidone and olanzapine are also good choices but should be used in lower doses.

Data for ziprasidone and aripiprazole dose administration in this population are not yet available. With regards to adverse effects, risperidone is associated with a higher risk of EPS and prolactin-related adverse effects than the other agents. If these are worrisome to the patient or family another agent may be a better first-line selection. On the other hand, olanzapine is associated with the greatest weight gain and metabolic disturbances and, thus, its use should be limited in patients who may be predisposed or concerned about these issues. Ziprasidone has the highest propensity to prolong the QTc interval, making it a last-line choice if risk factors are present. Quetiapine will most likely produce the greatest amount of sedation, possibly interfering with school or work. However, patients and families need to be aware that this is transient and are likely to dissipate after the first week. Aripiprazole may be associated with the highest risk of gastrointestinal complaints, but these usually decrease after the first few weeks.

In conclusion, few efficacy and safety data are available in first-episode patients; however, all agents can be expected to be efficacious in this population and have heterogeneous adverse effect profiles. Clinicians need to keep in mind that many of the listed adverse effects (i.e. prolactin-related adverse effects, weight gain, sedation) do occur more frequently and are more problematic in younger patients. Thus, careful attention should be made to drug selection and the lowest possible doses should be used.

4. Depression and Suicide Risk

Patients with schizophrenia are known to exhibit a high prevalence of depressive symptoms early in the course of illness.[178-182] In fact, depressive symptoms are among the earliest prodromal signs of schizophrenia to occur and around 50–80% of patients experience a depressed mood prior to the first positive symptoms.[7] Depressive symptoms early in the course of schizophrenia are highly associated with a family history of unipolar affective illness.[183] In a recent study, hippocampal fissure size was significantly associated with anxiety-depressive symptoms during the early onset of schizophrenia illness. This association between larger hippocampal fissure size and depressive symptoms may suggest that underlying hippocampal abnormalities may be a predisposing factor for increased stress sensitivity.[184] Nonetheless, high rates of depressive symptoms have implications on the patient's quality of life and the risk for suicide.[185]

Depressive symptoms in schizophrenia are frequently associated with suicidal ideation and behaviour.[186-188] Suicidal behaviour is frequent among patients with schizophrenia and an estimated 10% of patients with this illness will commit suicide.[189-191] It is known that suicidal rates are highest during the first weeks following discharge from the hospital and that young patients with first-episode schizophrenia are a particularly high-risk group.[192-194] Feelings of hopelessness in a first-episode population have been predictive of suicidal behaviour in the year following diagnosis[181] and first admission patients who had a current suicide attempt have significantly higher rates of depressive symptoms than those with past attempt only.[195] Other risk factors for suicide include male sex, Caucasian race, social isolation, poor psychosocial functioning, substance abuse, and previous suicide attempts or behaviour.[189] Furthermore, suicidal attempts are generally not planned and mostly occur as impulsive behaviour in patients with schizophrenia.[196] Thus, it is often difficult to predict or intervene on the basis of risk factors or planning behaviour.

In first-episode schizophrenia treated with antipsychotics, depressive symptoms may improve partially as a result of illness improvement or direct antidepressant effects of newer antipsychotics; however, some patients may require antidepressant medication in the early weeks of their hospitalisation. In fact, depressive symptoms correlate more with positive and negative symptoms than with EPS and may represent a core part of the acute illness or may occur as a subjective reaction to the experience of psychotic decompensation.[197] Depressive symptoms were actually worse at 3 months following treatment in one first-episode study, but were found to be significantly improved by 1 year.[193] Another

study also found rates of depressive symptoms during an acute psychotic phase to be significantly higher in first-episode versus multiple-episode patients, which was evident throughout the year following the episode, even during treatment.[198] Thus, early and appropriate management of first-episode schizophrenia symptoms should aim to address depressive symptomatology appropriately.

Very few studies have addressed depressive symptomatology and response to treatment in the first-episode schizophrenia population. Most data for depressive symptoms in first-episode schizophrenia are with olanzapine treatment. In a few recent nonrandomised, open-label, comparative studies of olanzapine versus haloperidol in acutely psychotic patients, olanzapine had significantly greater improvements in depressive symptoms compared with haloperidol.[40,199] A factor analysis of olanzapine compared with haloperidol treatment using randomised, double-blind clinical trials also found superiority of olanzapine; however, these data were not from first-episode patients.[200] No published randomised trials are available addressing suicide risk in first-episode patients treated with antipsychotics; however, a recently published trial (InterSept [International Suicide Prevention Trial]) has found the suicide rate in patients who were considered high risk for suicide to be lower in those treated with clozapine than with olanzapine.[201] Clozapine is generally not recommended nor routinely used in first-episode schizophrenia; however, it is worth noting that a case report exists for a first-episode schizophrenia patient who had severe depressive symptomatology and suicidal thoughts and attempts, and had an excellent recovery when treated initially with clozapine as part of InterSept.[202]

The differential effects of the SGAs in first-episode schizophrenia and their specific effects on depressive symptoms and suicide remain unknown. However, it does appear that SGAs may offer some benefits as compared with FGAs in patients with first-episode schizophrenia with depressive symptoms or suicidal tendencies and impulsiveness.

5. Safety Issues in Emergency Treatment

Psychiatric emergencies are often seen in emergency departments, but may also occur in the psychiatric unit, a medical facility or the outpatient setting. Most psychiatric emergencies require both pharmacological and psychotherapeutic interventions. The psychiatrist must often make decisions based on limited information or patient history. Each US state has a statute that requires a physician to detain patients involuntarily in a psychiatric facility if the patient is judged to be dangerous to self or others. Such patients may be treated against their will; however, they cannot be medicated in the long term without their consent unless a court order is obtained in most US states. Patients who are nonviolent but do not take care of their physical needs secondary to their psychosis may still represent a threat to themselves or others, but this decision is often based on clinical judgment. In first-episode psychosis, many patients will first present to their general practitioners; however, it has been reported that 13% of first-episode patients will present with acute symptoms to the emergency setting.[203]

The evolution of acute psychotic management has evolved dramatically over the past 20 years. While antipsychotic treatment is the mainstay of stabilisation, these medications given orally do not provide symptom relief (for positive symptoms) until after several weeks of treatment. Rapid tranquilisation with antipsychotic medications had been routinely used in the past for the acute management of psychosis with patients receiving either oral or parenteral injections of FGAs numerous times daily, although the outcomes of this type of therapy have not been always favourable.[204] In the 1980s, a movement towards using oral agents became more widely used as EPS were noted to be significantly higher with parenteral injections.[205] However, there appears no advantage to either high doses or parenteral administration of antipsychotics over lower, oral doses.[204,206] In the 1990s, the combination of an FGA and a benzodiazapine became fashionable on the basis of data that suggested the combination produced the most rapid tranquilisation.[207]

The introduction of the SGAs in the mid to late 1990s has transformed the way patients with schizophrenia are treated. While EPS were once believed to be an intrinsic part of the treatment of patients with psychotic symptoms, this is no longer believed to be true with the new class of medications. However, these medications lack the antipsychotic effect (perhaps a composite of antipsychotic-induced deficits and indirect sedation) of FGAs and may not be sufficient as sole agents in the first few days of stabilisation during acute admission for routine dose administration. This is especially true when considering the low relative doses of SGAs commonly employed. Foster et al.[208] noted that benzodiazepine use, notably lorazepam, was an excellent alternative to antipsychotic treatment and was no different than haloperidol for symptom ratings. Patients themselves rate benzodiazepines as first choice and antipsychotics last, as reported in a psychiatric emergency service survey.[209] Many reports have recommended the use of short-term benzodiazepines in combination with SGAs as a better alternative than traditional treatment options in acute hospital admissions as they avoid the distressing EPS associated with moderate to high doses of FGA treatment[210-212] as well as the 'zombie-like' effect of these medications.[213]

Nevertheless, very little data from clinical studies or real-world use of the combination of SGA and benzodiazepine use have been published. Recently, Currier and Simpson[214] found similar efficacy of oral risperidone 2mg versus intramuscular haloperidol 5mg, both in combination with lorazepam 2mg for the acute treatment of psychotic agitation. Patients treated with the SGA did not experience any untoward adverse effects or EPS. Another prospective naturalistic study examined the impact of replacing standard antipsychotics with SGAs in an emergency care setting. The investigators found that there were no significant differences in symptoms, the rate of aggressive or violent behaviour, or length of stay between the groups in this mirror image study. They did report much fewer adverse effects with SGAs.[215]

Intramuscular formulations of SGAs are becoming available. Intramuscular ziprasidone has been approved for acute treatment in agitated psychotic patients and has been found to be more effective in reducing symptoms of acute psychosis as well as being better tolerated and having fewer EPS than intramuscular haloperidol.[216] Intramuscular olanzapine has also been studied and showed better efficacy and tolerability than intramuscular haloperidol in clinical trials.[217]

While current guidelines may recommend SGAs as first-line treatment, with the addition of benzodiazepines for psychotic agitation if necessary, documentation of the use or success of this combination is lacking.[218] Furthermore, a recent survey of psychiatric emergency services in the US found that approximately 70% of 56 sites continue to advocate the use of an intramuscular cocktail consisting typically of haloperidol, a benzodiazepine and an anticholinergic agent.[219]

Because first-episode patients have a high risk of adverse effects, particularly EPS, high doses of haloperidol for acute or short-term treatment should be avoided.

6. Medication Nonadherence

Long-term goals of antipsychotic treatment include preventing the onset of acute episodes of psychosis and maintenance of positive symptom treatment at current levels. Negative symptoms and cognitive deficits generally remain after a psychotic episode. Thus, these also become a focus of long-term rehabilitation. Yet, inevitably, relapses are common during the course of schizophrenia. Weiden and Olfson[220] estimated that the average relapse rate on FGAs was 3.5% per month, thus resulting in a 42% annual relapse rate. Many studies have shown that the most powerful predictor of relapse and rehospitalisation is adherence with drug treatment.[221-224]

Patients with schizophrenia are often known to be noncompliant with medication; however, this is a prevalent problem in many somatic and psychiatric disorders.[225] For example, patients with asthma and rheumatoid arthritis, two disorders where direct ben-

efits are generally observed with treatment, typically report nonadherence and partial adherence of around 50%.[226,227] Other psychiatric disorders also have high rates, with 44% of patients typically discontinuing antidepressant treatment within the first 3 months.[228] Adherence in schizophrenia is especially problematic because identification of missed doses is difficult, there are no immediate consequences of missing a dose, and many patients have neurocognitive deficits and paranoid symptoms. Adverse effects with antipsychotic treatment are also a major contributing factor to treatment nonadherence in this disorder.

Specific factors have predicted higher rates of nonadherence. Younger, grandiose, substance abusing and deficit patients have more difficulty with adherence. Adherence is difficult to quantify, measure and study because adherence is rarely an all-or-nothing phenomenon, but may include mistakes in dose administration and timing, omitting doses or taking medications that are not prescribed. Estimates of nonadherence on FGAs range from approximately 24% to 88% (with a mean of approximately 50%) of patients with schizophrenia.[229] Patients who are noncompliant have an approximately 4-fold greater risk of relapse than those who are compliant. Physicians often overestimate the adherence of their patients, which, in turn, does not allow them to consider nonadherence as a likely explanation for treatment failures.

Between 25% and 66% of patients who discontinue prescribed antipsychotic therapy cite adverse effects as the primary reason for nonadherence.[230] Higher subjective measurements of adverse effects as well as physician ratings have been associated with higher rates of nonadherence. EPS (most notably akathisia), sexual dysfunction and weight gain, are the adverse effects that lead to the greatest nonadherence.[49] SGAs are associated with better rates of adherence, which is most likely to be attributable to a lower incidence of dysphoria and EPS.[231] This leads to lower rates of relapse and rehospitalisation, improving patient care and reducing overall costs.[232] Yet, while pharmacy prescription data have found higher rates of adherence with SGAs compared with rates with FGAs, it appears that 45% of patients may continue to be nonadherent.[233] A good relationship between the patient and physician is important to establish rapport and trust, the groundwork for enhancing patients' acceptance of the therapy. Patient and family education, including expectations and potential adverse effects, is important. The emergent of adverse events should be taken seriously and treated immediately.

Very little data are available that assess adherence in first-episode patients. However, there is some evidence that younger patients are more likely to be nonadherent than older patients.[228,234,235] One recent study examined predictors of medication discontinuation in 118 first-episode schizophrenia patients. Twenty-six percent stopped antipsychotics during the first year of treatment, despite ongoing efforts by the research team to educate patients and their families about schizophrenia and to maintain adherence to antipsychotic treatment. EPS, depression and poor cognitive functioning were the highest predictors of medication nonadherence in this sample.[236] Another study assessing antipsychotic adherence in an early psychosis programme found that 59% of patients were inadequately adherent to low-dose antipsychotics. Not surprisingly, the group of patients who were nonadherent experienced higher rates of relapse, more drug use and a poorer quality of life.[8] Nonadherence early in the course of illness has been shown to negatively impact prognosis, as was convincingly seen in a 20-year follow-up study of first-episode patients[237] as well as in other studies.[9,238] Patients who are nonadherent may also be more likely to engage in assaultive and dangerous behaviours and may have a higher risk of suicide.[239] Thus, it is imperative for the safety and long-term outcomes of patients with first-episode schizophrenia that medication adherence be a primary concern. Treatment strategies that may improve medication adherence may be patient related (cognitive therapy, education about the illness, education about the benefits of treatment, memory aids, e.g. telephone reminders and medication timers, involvement of patient in therapeutic alliance), physician related (education on the impact and manage-

ment of adverse effects, use of a 'patient-centred' approach), social environment related (education and support for the patient's family, improved access to mental health services including assertive case management, home visits and convenient appointments, more attractive clinic environment, improved coordination between different service providers) and treatment related (minimising complexity of regimen, titration to optimum dose, minimising impact of adverse effects on patient's life, providing clear instructions on medication use, selection of antipsychotic with minimal adverse effects, use of long-acting injectable antipsychotic).[230,240,241]

SGAs may be associated with higher rates of medication adherence primarily by decreasing the adverse effect burden. SGAs are beginning to be approved and marketed in long-acting injectable formulations, which may lead to better long-term outcomes secondary to improved adherence rates. Risperidone is the first and only SGA that has been marketed as a long-acting microsphere technology thus far. More data are needed for SGAs and long-acting formulations in the first-episode population regarding their effects on adherence and improved outcomes.

7. Conclusion

Early and appropriate treatment with antipsychotics in patients with first-episode schizophrenia is an important strategy. There are many issues regarding safety that should be considered and properly addressed. Depressive symptoms and suicidal behaviour commonly occur in first-episode patients and every effort should be made to treat and minimise these symptoms. There are important issues and considerations in young and first-episode patients that should also be considered in the emergency treatment setting and for minimising medication nonadherence in this population. Most importantly, adverse effects should be considered, minimised and addressed. While FGAs and SGAs both appear to offer similar efficacy for amelioration of positive symptoms in first-episode patients, SGAs may offer better tolerability, specifically regarding EPS/tardive dyskinesia risk and some prolactin-sparing benefits. However, these medications do cause a host of adverse effects, including weight gain, metabolic disturbances, QTc interval prolongation and prolactin-related adverse effects, which are important considerations for both the short- and long-term safety of patients with schizophrenia being treated with the SGA medications. This antipsychotic class is, however, very heterogeneous regarding adverse effect profiles and medications should be optimised in a highly individualised way to maximise treatment outcomes and minimise tolerability and safety concerns. At some point in their lives, these patients are likely to experience periods of depression, suicidal behaviours, adverse effects and nonadherence, and every effort should be made to minimise or prevent these occurrences. Thus, safety concerns in this group of young patients, at the beginning of their first psychotic episode, are a major issue as they are starting a journey of antipsychotic treatment that is likely to last for the remainder of their lives.

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