Psychiatric Quarterly, Vol. 73, No. 4, Winter 2002 (© 2002)

SAFETY AND TOLERABILITY: HOW DO NEWER GENERATION "ATYPICAL" ANTIPSYCHOTICS COMPARE?

Rajiv Tandon, M.D.

Previously, clinicians worked with antipsychotic drugs that almost invariably caused extrapyramidal side effects (EPS) at the dose at which they were clinically effective. By definition, all newer generation *atypical* antipsychotic agents are significantly better than conventional agents with regard to EPS; i.e., they are clinically effective at doses at which they do not cause EPS. This EPS advantage of atypical antipsychotics translates into several important clinical benefits, including better negative symptom efficacy, lesser dysphoria, less impaired cognition, and a lower risk of tardive dyskinesia; in fact, this "EPS advantage" is the principal basis of the many clinical advantages provided by the class of atypical antipsychotics. While all atypical agents share this "EPS advantage," there are important differences between these agents with regard to the ease and consistency with which this EPS advantage can be realized. Pharmacologically, different atypical antipsychotics differ; these differences translate into differences in their side effect profiles. Five atypical antipsychotics are currently available: clozapine, risperidone, olanzapine, quetiapine, and ziprasidone. Meaningful differences between these agents with regard to weight gain, sedation, anticholinergic side effects, cardiovascular issues,

Rajiv Tandon, M.D., is a Professor of Psychiatry at University of Michigan Medical Center, Ann Arbor, MI.

Address correspondence to Rajiv Tandon, University of Michigan Medical Center, Ann Arbor, MI 48109-0120; e-mail: rtandon@umich.edu.

0033-2720/02/1200-0297/0

endocrine side effects, hepatic and sexual issues, will be considered and their clinical implications discussed.

KEY WORDS: antipsychotics; side effects; treatment; schizophrenia; pharmacology.

INTRODUCTION

Approximately forty antipsychotic agents are available around the world, of which twenty are approved for use in the U.S.A. These agents, primarily utilized for the treatment of schizophrenia and other psychotic disorders, first became available fifty years ago. Originally these agents were referred to as *major tranquilizers* because of their significant sedative properties or more commonly as *neuroleptics* because of their propensity to cause parkinsonian side effects. In fact, these agents were identified as much by this extrapyramidal side effect (EPS) as by their efficacy in treating psychotic symptoms and until recently, EPS were considered an unavoidable byproduct of antipsychotic treatment. Over the past decade, five *atypical* or *newer generation* antipsychotic agents have become available in the U.S.A.; these agents are principally distinguished by their at-least equivalent antipsychotic efficacy to the *older-generation conventional* neuroleptics with a much lower propensity to cause EPS (Figure 1).

Extrapyramidal side effects have a pervasive negative impact on treatment. Acute dystonic reactions are uncomfortable and frightening to the patient, and lead to early discontinuation of therapy and worse long-term outcome. 'Parkinsonian' bradykinesia and rigidity contribute secondary negative symptoms to the illness by reducing facial expression, vocal intonation, and affective responsiveness (1). Early development of these motor side effects has been correlated with subsequent development of tardive dyskinesia (2). Akathisia may be experienced by patients as restlessness, anxiety, agitation, insomnia, or generalized discomfort. Akathisia is frequently overlooked among medication side effects by clinicians and patients alike, but is strongly associated with premature termination of treatment (3). The adverse effect of EPS on cognitive function has only recently been recognized (4). EPS are now known to have a direct, adverse effect on cognition. In addition to this direct effect, EPS are commonly treated with anticholinergic medications, which further impair cognitive function.

The lower propensity of the five newer generation "atypical" antipsychotics to cause EPS is therefore associated with multiple benefits, including a broader spectrum of efficacy (greater improvement in

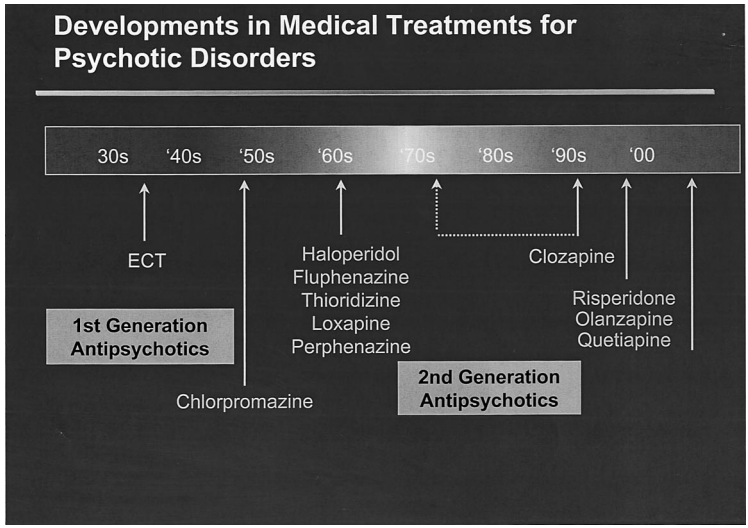

FIGURE 1. Antipsychotics in the United States—historical perspective.

negative, cognitive, and depressive symptoms), a lower risk of tardive dyskinesia (about a 90% reduction over 1–2 years), and improved compliance (Figure 2) (5). These advantages of the newer generation "atypical" agents over the older "conventional" neuroleptics explain their

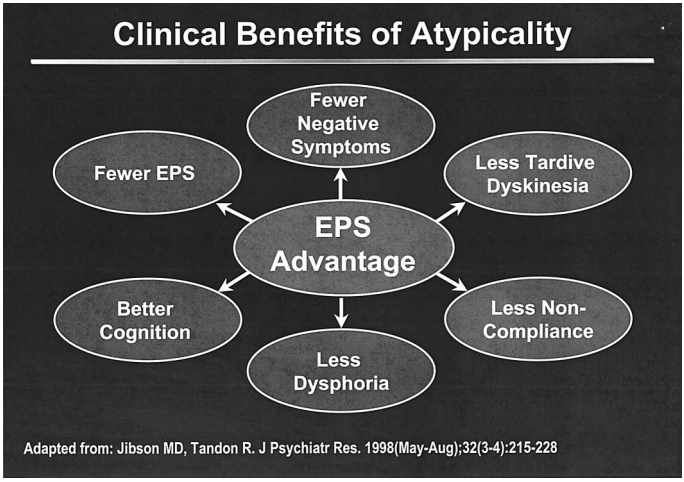

FIGURE 2. Benefits of atypical antipsychotics: Relationship to achieve antipsychotic effect without EPS.

greater utilization by clinicians in the U.S.A., where they collectively constitute approximately 80% of all antipsychotics prescribed.

The Newer Generation "Atypical" Antipsychotics: Are They All the Same?

Five newer generation antipsychotics are currently available in the U.S.A.: clozapine, risperidone, olanzapine, quetiapine, and ziprasidone (in order of their introduction, Figure 1). As noted above, this group of agents is clinically distinguished from the older "neuroleptics" by at least equivalent antipsychotic potency, broader spectrum of efficacy (negative, cognitive, and mood symptoms), and a lower risk of EPS and tardive dyskinesia (Figure 2). Clozapine, the first among these agents to become available, was additionally found to be superior in efficacy to conventional "neuroleptics" in treating otherwise refractory schizophrenia patients (6–8). However, because of its many significant adverse effects (Table 3) and the need for periodic hematological monitoring, its use is reserved for otherwise treatment-refractory patients.

Because of an overall better safety/tolerability profile than clozapine, the other four agents (risperidone, olanzapine, quetiapine, and ziprasidone) are often referred to as "first-line atypical antipsychotics." A number of studies have been undertaken to determine if there are significant differences in efficacy, speed of response, and stability of remission among these medications. To date, no clear pattern of superior efficacy among these agents has emerged (9–14); in fact, each of these "first-line atypical antipsychotic drugs" appears to have equivalent efficacy in reducing overall psychopathology as also severity of specific symptom domains (positive, negative, affective) in patients with schizophrenia. Appropriate dosing with each of these agents (Table 4) is critical to optimizing efficacy.

While sharing the clinical attributes of a broader spectrum of efficacy and lower risk of EPS and tardive dyskinesia, these four agents are chemically and pharmacologically distinct from one another, and each consequently has a unique side effect profile. The remainder of this paper explores the relationship between the neuropharmacological profiles of currently available atypical antipsychotic agents and their clinical attributes (particularly, their side effects). A strategy to incorporate this information while selecting between different atypical antipsychotic agents is then summarized.

There are similarities and differences between the receptor-blocking profiles of conventional and atypical antipsychotics and between different atypical antipsychotics. There are also known differences in the

TABLE 1
Pharmacological Profile of Atypical Antipsychotics

Clozapine:	several properties (D-1, D-2, D-3, D-4, 5HT-2A, 5HT-2C, 5HT-3, ACh, H-1, NE)
Risperidone:	D-2 + 5HT-2A + 5HT-2C + alpha-1 NE
Olanzapine:	D-2 + 5HT-2A + 5HT-2C + (alpha-1 NE) + (M-1) + H-1
Quetiapine:	D-2 + 5HT-2A + alpha-1 NE + H-1
Ziprasidone:	D-2 + 5HT-2A + (increased NE, 5HT, 5HT-1A)

Note. All the "atypical" antipsychotics retain Dopamine D-2 receptor blockade, deliberately add Serotonin 5HT-2A receptor blockade that is more potent than D-2 blockade. What else they add differs from agent to agent.

clinical profiles of conventional and atypical antipsychotics and in the side effect profiles of different atypical agents. There is a fair, though not perfect, correspondence between the pharmacological profiles of the different antipsychotic agents and their clinical attributes (efficacy and side effects). Based on a comparison of the receptor-blocking profiles of the different antipsychotic agents, one can fairly predict similarities and differences in their clinical attributes (Tables 1–3).

The pharmacological (principally receptor-blocking) profiles of the five currently available atypical antipsychotic agents are summarized in Table 1. Pharmacological activities in parentheses refer to weaker, but clinically relevant, properties. The letter refers to the neurotransmitter (D = dopamine, 5HT = serotonin, ACh = acetylcholine, H = histamine, NE = norepinephrine) and the number (eg., 1 or 2A) that follows refers to the receptor of that neurotransmitter. All activities noted refer to receptor blockade except for the activities described in parentheses for ziprasidone. As can be seen from the table, all atypical antipsychotic agents retain the property of dopamine D-2 blockade (albeit to differing extents) that characterizes the older conventional agents. All five newer generation antipsychotics add more potent (than D-2) blockade of one of the serotonin receptors (the 5HT-2A receptor); in fact, these five agents block the 5HT2A receptor about ten times as potently as the D2 receptor and this is the one property that differentiates the group of atypical antipsychotics from the older conventional antipsychotics (12,13,15). In addition to these shared attributes (D-2 blockade and more potent 5HT-2A blockade), the atypicals differ in their other pharmacological properties.

The likely clinical implications of antagonizing various neurotransmitter receptors are summarized in Table 2 (12,16). All known antipsychotic agents in the world (including the 20 approved antipsychotic

TABLE 2
Clinical Implications of Blockade of Various Receptors by Antipsychotics

Receptors	*Possible Benefits*	*Possible Side Effects*
Dopamine D_2 receptor	Antipsychotic effect Efficacy on positive symptoms Efficacy on agitation	Extrapyramidal movement disorders (EPS), (dystonia, Parkinsonism, akathisia, tardive dyskinesia) Endocrine changes (prolactin elevation causing galactorrhea, gynecomastia, menstrual changes, sexual dysfunction)
Serotonin 5HT receptors		
$5HT_{2A}$ receptors	Reduced EPS	Sexual disturbances
$5HT_{2C}$ receptors	Not definitely known	Weight gain
Histamine H_1 receptor	Not definitely known	Sedation, weight gain
Muscarinic receptor	Not definitely known	Blurred vision, dry mouth, constipation, urinary retention, sinus tachycardia, memory dysfunction
a_1-Adrenergic receptor	Not definitely known	Postural hypotension, dizziness

agents in the U.S.A.) block the dopamine D-2 receptor. Consequently, D-2 blockade (presumably in the mesolimbic dopamine tract) can presently be considered as being essential for antipsychotic activity. Dopamine-2 blockade in the nigrostriatal dopamine system, however, results in extrapyramidal side effects (EPS) and D2 blockade in the tubero-infundibular system results in prolactin elevation and related side effects (menstrual irregularities, sexual dysfunction, gynaecomastia, etc.).

In recent years, the pervasiveness and tightness of D-2 blockade (rather than mere presence or absence of D-2 blockade) have been related to the antipsychotic efficacy of antipsychotic agents and their propensity to cause EPS and prolactin elevation (17,18). It has been suggested that greater than 60% blockade of D-2 receptors is necessary for antipsychotic activity, whereas more than 70% blockade results in prolactin elevation and greater than 80% blockade results in EPS. It has

TABLE 3
Side Effect Profiles of the Newer Generation "Atypical Antipsychotic Agents"

	Typical Neuroleptic	*Clozapine (Clozaril™)*	*Risperidone (Risperdal™)*	*Olanzapine (Zyprexa™)*	*Quetiapine (Seroquel™)*	*Ziprasidone (Geodon™)*
Agranulocytosis	± to +	++	±	±	±	±
Anticholinergic	± to +++	+++	±	+	±	±
ALT/AST elevation	± to +	+	±	+	±	±
EPS at low doses	± to ++	±	±	±	±	±
Dose-dependent EPS	+++	0	++	+	0	+
Orthostatic hypotension	+ to +++	+++	++	+	++	+
Prolactin elevation	++ to +++	0	+++	±	±	±
QTc prolongation	± to ++	+	±	±	±	+
Sedation	+ to +++	+++	+	++	++	+
Seizures	± to +	++	±	±	±	±
Tardive dyskinesia	+++	0	±	±	±	±
Weight gain	± to ++	+++	++	+++	++	±

Note. 0: Absent; ±: Minimal; +: Mild or Low risk; ++: Moderate; +++: Severe; ALT: alanine aminotransferase; AST: aspartate aminotransferase; EPS: extrapyramidal side effects.

also been suggested that tighter blockade of the dopamine D2 receptor (more difficult for endogenous brain dopamine to displace) results in a higher risk of EPS.

5HT-2A receptor blockade more potent than D-2 receptor blockade substantially reduces the risk of EPS associated with such D-2 blockade (15). Thus it may be possible to achieve an antipsychotic effect (for which you need D-2 blockade) without EPS (which D-2 blockade would cause in the absence of more potent 5HT-2A receptor blockade). This attribute of the newer generation of antipsychotics is believed to explain their ability to achieve an antipsychotic effect with a much lower risk of EPS than with conventional agents. The relative risk of EPS with the various antipsychotic agents at clinically effective doses is perhaps best explained by a combination of 5HT2A/D2 blockade, pervasiveness and tightness/looseness of dopamine receptor blockade. The clinical implications (mainly side effects) of other receptor-blocking properties are also summarized in Table 2; an effort is made to stay very close to what we know well without speculation.

Table 3 summarizes how the five atypical agents compare to each other and typical neuroleptics with regard to various side effects. Anticholinergic side effects (peripheral, cardiac, and central) are explained by the degree of antimuscarinic anticholinergic activity *in-vivo* (12,16). Dizziness and postural hypotension (necessitating dose titration) are best explained by alpha-1 NE blockade. Sedation is explained principally by antihistaminic activity, but anticholinergic and D-2 antagonism properties also contribute. Weight gain is best explained by a combination of 5HT-2C blockade, H-1 blockade, and D-2 blockade. Factors contributing to EPS and prolactin elevation have been considered previously; other side effects are not easily explained on the basis of known pharmacological activities. Specific side effects are now briefly considered along with the relative propensity of various newer generation agents to cause them.

Acute Extrapyramidal Side Effects (EPS)

By definition, all "atypical" antipsychotics are less likely than conventional antipsychotics to cause EPS; in fact, that is how they got the "atypical" label. There are, however, differences between various atypical agents with regard to the ease and consistency with which EPS can be avoided at clinically effective doses. Among the five currently available newer generation antipsychotics, the hierarchy of EPS risk is risperidone > olanzapine = ziprasidone > quetiapine > clozapine. Clinically, these differences are most relevant in vulnerable populations,

(elderly, adolescents, patients with Parkinson's disease with psychosis, etc.). These differences also become relevant to optimal dosing of these agents (Table 4) so as to obtain an acceptable antipsychotic effect without EPS as also in circumstances when an atypical agent is used concurrently with a conventional agent (here, the analogy of Parkinson's disease with psychosis is useful). Since the absence of EPS principally contributes to the many benefits of atypicality (Figure 2), it is essential that EPS be avoided. Furthermore, EPS should be avoided *without use of anticholinergic antiparkinsonian medication*, as most benefits (eg, cognitive advantage, lower risk of tardive dyskinesia, etc.) are lost when these agents are utilized.

Weight Gain and Related Side Effects

Weight gain is emerging as one of the most significant side effects associated with atypical antipsychotic therapy (19–21). Weight gain is associated with an increased risk of diabetes mellitus and hyperlipidemia (all associated with an increase risk of coronary heart disease); and there are increasing reports of these "complications" in patients with schizophrenia receiving atypical antipsychotics. The relative propensity to cause weight gain among the newer generation antipsychotics is clozapine > olanzapine > risperidone = quetiapine > ziprasidone; the average weight gain with one-year treatment ranges from 33 lbs (clozapine) to 2 lbs (ziprasidone) with olanzapine (25 lbs) and risperidone/quetiapine (4–8 lbs) in between. There are increasing reports of new-onset diabetes mellitus, exacerbation of existing diabetes, and cases of diabetic ketoacidosis in association with atypical antipsychotic treatment (particularly with clozapine and olanzapine). Although it is premature to conclude that olanzapine, clozapine, or other atypical agents *cause* diabetes, attention to this issue is warranted.

QTc Prolongation

In the past decade, the issue of prolongation of the QTc (QT interval on the EKG corrected for heart-rate) has received increasing scrutiny from the Food and Drug Administration (FDA) and five different medications have been withdrawn from the market and several others have received different kinds of product warnings because of this issue (22,23). Prolongation of the QTc (generally indicative of slowed ventricular repolarization) has been associated with an increased risk of Toursade de Pointes (a polymorphic ventricular tachycardia), which in turn has been associated with other potentially fatal ventricular arrhythmias.

Whereas all the newer generation antipsychotics (like the older generation conventional agents) prolong the QTc interval, they do so to different extents. Several methods are employed to rate-correct the QT interval, and therefore there are several QTc's; however, among the newer generation agents, the usual hierarchy of QTc prolongation is ziprasidone = clozapine > quetiapine ≥ risperidone ≥ olanzapine. The QTc prolongation associated with olanzapine, risperidone, and quetiapine are in the range of that associated with haloperidol (which has hitherto been considered to cause clinically irrelevant QT prolongation). The QTc prolongation associated with ziprasidone is intermediate between that of haloperidol and thioridazine. The precise relevance of the degree of QTc prolongation associated with the various atypical agents is unclear, and no increase in rates of Toursades or sudden cardiac deaths has been found with any of these agents.

Sedation

All newer generation antipsychotics and conventional agents are sedating (hence the old term "tranquilizer"), but cause different degrees of sedation. Among the newer generation agents, the hierarchy of producing sedation is clozapine > quetiapine > olanzapine > risperidone > ziprasidone. Sedation is most prominent in the early stages of antipsychotic therapy and some degree of tolerance develops over time.

Prolactin Elevation and Related Side Effects

The older "conventional" antipsychotic agents all increased levels of the hormone, prolactin; among the newer generation agents, risperidone alone consistently increases prolactin levels. While increased prolactin levels have been associated with sexual dysfunction, menstrual irregularities, etc., an increased occurrence of these clinical symptoms in risperidone-treated (in contrast to other atypical-treated) patients has not been clearly demonstrated. It is suggested that prolactin-related clinical side effects occur in about 25–30% of patients with increased levels of prolactin (24,25).

Hypotension

All antipsychotic agents cause hypotension, particularly postural hypotension, although they do so to different extents. Among the newer generation antipsychotics, the hierarchy of producing hypotension is clozapine > quetiapine > risperidone > olanzapine = ziprasidone.

Hypotension tends to be most prominent in the early stages of treatment with tolerance developing over time. Adequate hydration mitigates the problem of hypotension, although agents that are associated with more hypotension are best titrated up to their target dose (over 2–3 days for risperidone and quetiapine, and over 1–2 weeks for clozapine).

Anticholinergic Side Effects

Because of varying degrees of intrinsic anticholinergic activity, different atypical antipsychotic agents cause varying degrees of anticholinergic side effects. The spectrum of anticholinergic side effects include peripheral symptoms (dryness of mouth, constipation, urinary retention, etc.), cardiovascular symptoms (tachycardia, increased risk of tachyarrhythmias, etc.) and cognitive symptoms (impaired learning and memory) (26,27). Among the newer generation antipsychotic agents, the hierarchy of anticholinergic side effects is clozapine $\gg$ olanzapine $>$ quetiapine $\geq$ risperidone/ziprasidone. It should be noted, however, that except for clozapine, the magnitude of anticholinergic side effects associated with the atypicals is much smaller than that associated with benztropine and trihexyphenidyl (oral anticholinergic agents used to prevent and treat antipsychotic-associated EPS). It is therefore critical that EPS be avoided without concomitant use of anticholinergic agents.

Miscellaneous Other Side Effects

A variety of other side effects have been reported in association with atypical antipsychotic treatment; these include elevated liver enzymes, acute pancreatitis, priapism, tardive dyskinesia, neuroleptic malignant syndrome, special sense adverse effects, etc. It is unclear if there are meaningful differences in rates of these side effects with the different atypical agents. It appears that rates of neuroleptic malignant syndrome and tardive dyskinesia are lower with newer-generation in contrast with conventional antipsychotic agents.

IN SUMMARY

Since the multiple benefits associated with atypical antipsychotic treatment are principally related to their ability to achieve an optimal antipsychotic effect without producing EPS, it is critical that atypical

agents be dosed in such a way that they produce an optimal antipsychotic effect without EPS and without the need for adjunctive anticholinergic treatment to treat such EPS. Although there is significant heterogeneity in treatment response and the optimal dose varies across individual patients, we have a fair body of evidence that guides appropriate dosing for the vast majority of patients. In the treatment of young adults suffering from schizophrenia, appropriate initial target doses for the five atypical agents and the maximum dose likely to benefit a majority of patients are summarized in Table 4. Appropriate dose ranges in

TABLE 4
The Atypical Antipsychotics (Summary)

Clozapine, Risperidone, Olanzapine, Quetiapine, Ziprasidone

1. Equivalent efficacy in treating psychotic symptoms in various disorders
   – clozapine is more effective in patients refractory to conventional antipsychotics
   – no other convincing evidence of differential efficacy among various atypical agents
   – broader spectrum of efficacy (negative, cognitive, and mood symptoms)
2. Significantly less likely than conventional agents to cause extrapyramidal side effects
   – ease and consistency with which efficacy without EPS is achieved varies from atypical to atypical
3. Multiple benefits (fewer negative symptoms, better cognition, less depression, lower risk of tardive dyskinesia) accompany this EPS advantage of atypical agents
   – Dosing is key to achieving this profile of optimal efficacy without EPS
   – Recommendations about dosing in young adult schizophrenia patients

Agent	*Initial dose to go up to*	*Maximum dose likely to be beneficial*
Clozapine:	400 mg/day	500 mg/day (level 370–500 ng/ml)
Risperidone:	(2!) 3–4 mg per day	6 mg/day
Olanzapine:	15–20 mg per day	30–40 mg/day! (outside FDA recommendations)
Quetiapine:	400–600 mg per day	800–1200 mg/day (>800 mg/day outside FDA guidelines)
Ziprasidone:	100–120 mg per day	160–200 mg/day? (>160 mg/day outside FDA guidelines)

   – lower doses in children, elderly, and other vulnerable populations
   – lower doses in patients with other diagnoses
4. Differ in propensity to cause other side effects (sedation, weight gain and related adverse effects, hypotension, cardiovascular, prolactin elevation and related adverse effects, etc.)

children, the elderly, and other vulnerable populations would be lower. Similarly, appropriate doses to treat nonschizophrenic conditions would also be lower than indicated.

Because of their superior adverse effect profiles, atypical agents are recommended over conventional antipsychotics. Since there is no evidence of differential efficacy between different first-line atypical agents, efficacy is not a factor in choosing between them. Differences in side effect profiles, however, allow selection of the initial antipsychotic based on the need to avoid the most undesirable side effects in each individual patient.

In summary, schizophrenia treatment involves the judicious use of multiple treatment modalities, of which pharmacology is among the most important. Primary goals of treatment are the rapid and complete control of active psychosis, avoidance of functional deterioration, and prevention of relapse; secondary objectives include minimizing side effects and optimizing function. Although numerous medication options are available, and treatment must be tailored to individual situations, the newer atypical antipsychotics have significant advantages in routine use over conventional agents. Despite their higher cost, the benefits of patient acceptance, reduced risk of side effects, and broader spectrum of activity make their use compelling. To maximize the benefits of atypical antipsychotics, the dose of medication should be carefully adjusted to achieve as complete a remission of psychotic symptoms as possible, without accompanying EPS or the use of anticholinergic medications to treat or prevent EPS (Figure 2). Differences in side effect profiles of atypical agents allow individualization of treatment. If dosing a particular newer generation antipsychotic to achieve an adequate antipsychotic effect with acceptable tolerability is unsuccessful, a change to an alternative atypical antipsychotic is indicated and will generally include a very gradual cross titration, during which the patient is never free of "antipsychotic cover."

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