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Extrapyramidal Symptoms with Atypical Antipsychotics

Incidence, Prevention and Management

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Contents

Abstract

The treatment of schizophrenia changed drastically with the discovery of antipsychotic medications in the 1950s, the release of clozapine in the US in 1989 and the subsequent development of the atypical or novel antipsychotics. These newer medications differ from their conventional counterparts, primarily based on their reduced risk of extrapyramidal symptoms (EPS). EPS can be categorised as acute (dystonia, akathisia and parkinsonism) and tardive (tardive dyskinesia and tardive dystonia) syndromes. They are thought to have a significant impact on subjective tolerability and adherence with antipsychotic therapy in addition to

impacting function. Unlike conventional antipsychotic medications, atypical antipsychotics have a significantly diminished risk of inducing acute EPS at recommended dose ranges. These drugs may also have a reduced risk of causing tardive dyskinesia and in some cases may have the ability to suppress pre-existing tardive dyskinesia.

This paper reviews the available evidence regarding the incidence of acute EPS and tardive syndromes with atypical antipsychotic therapy. Estimates of incidence are subject to several confounds, including differing methods for detection and diagnosis of EPS, pretreatment effects and issues surrounding the administration of antipsychotic medications. The treatment of acute EPS and tardive dyskinesia now includes atypical antipsychotic therapy itself, although other adjunctive strategies such as antioxidants have also shown promise in preliminary trials.

The use of atypical antipsychotics as first line therapy for the treatment of schizophrenia is based largely on their reduced risk of EPS compared with conventional antipsychotics. Nevertheless, EPS with these drugs can occur, particularly when prescribed at high doses. The EPS advantages offered by the atypical antipsychotics must be balanced against other important adverse effects, such as weight gain and diabetes mellitus, now known to be associated with these drugs.

The association between treatment with antipsychotic medications and extrapyramidal symptoms (EPS) was discovered along with their first use in the 1950s. Indeed, the term 'neuroleptic' (meaning 'to seize or hold the neuron') was coined to describe the neurological adverse effects of conventional antipsychotic medications rather than their therapeutic or psychotropic effects. Antagonism of the dopamine D_2 receptor is believed to mediate both the antipsychotic action and the EPS of antipsychotic medications. Positron emission tomography studies have revealed that approximately 60–70% of D_2 receptor blockade is needed for conventional antipsychotics to be efficacious; however, ≥75–80% D_2 blockade results in acute EPS.[1] This therapeutic window is the most narrow with the high potency conventional antipsychotics, for which therapeutic activity and EPS are often inextricable. Consequently, in the neuroleptic era, preclinical screening of antipsychotic efficacy depended on the ability of drugs to induce catalepsy in animals. In addition, in the clinical setting it was standard practice to increase the dose of conventional antipsychotics to the 'neuroleptic threshold' (the dose at which EPS occurred) and then wait for a therapeutic response.

The time-honored expectation that antipsychotic therapy would be associated with EPS changed with the advent of clozapine. Early experience with this drug revealed that it was efficacious without causing EPS, though this violation of 'neuroleptic dogma' limited its widespread clinical use.[2] Clozapine was removed from the European market in 1975 as a result of several deaths associated with clozapine-induced agranulocytosis, but was later approved in the US for the treatment of refractory schizophrenia in 1990. However, despite robust efficacy in refractory populations,[3] the adverse effect profile of clozapine (agranulocytosis, seizures, sedation, sialorrhoea, orthostasis and tachycardia) and the requirement for weekly blood monitoring continues to limit its use to only 1–15% of patients,[4,5] although up to 40% of patients with schizophrenia are considered treatment refractory.[6] The 'atypical' antipsychotic niche formed by clozapine sparked a subsequent effort to develop other compounds that might replicate the therapeutic efficacy of clozapine without its adverse effects, while maintaining a much lower EPS risk relative to conventional antipsychotics. To date, the atypical or novel antipsychotic medications released in the US include clozapine, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole.

The defining characteristic of an atypical antipsychotic is its lower risk of inducing EPS.[7] This

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lower risk offers a potentially significant benefit for patients with psychotic disorders given that EPS can be uncomfortable, disfiguring and functionally impairing. As a result, EPS are thought to be an important cause of treatment refusal and nonadherence,[8,9] as well as psychiatric malpractice lawsuits.[10,11] While atypical antipsychotics are thought to be associated with a significantly reduced EPS risk, this risk is not zero and recent evidence calls into question to what extent these drugs are clearly superior to conventional antipsychotics with respect to EPS liability.[12,13] This article provides a review of atypical antipsychotic-associated EPS and discusses the efficacy of available therapeutic interventions. A search was conducted in Medline (1966–June 2003) using the keywords 'clozapine', 'olanzapine', 'quetiapine', 'risperidone', 'ziprasidone', 'aripiprazole', 'tardive dyskinesia and 'extrapyramidal symptom'.

1. Extrapyramidal Symptoms (EPS) Defined

The term 'extrapyramidal' pertains to the motor system distinct from the corticospinal (pyramidal) tract and composed of the basal ganglia (caudate, putamen, globus pallidus), subthalamic nucleus, substantia nigra, red nucleus and brain stem reticular formation. The 'nigrostriatal' dopamine pathway traverses these anatomical structures and D_2 blockade in this region is thought to give rise to EPS. Antipsychotic-induced EPS includes a variety of different iatrogenic movement disorders that can be divided into acute and tardive syndromes. Acute syndromes are those that develop within hours or days of antipsychotic treatment and include acute dystonia, akathisia and parkinsonism. Tardive dyskinesia and tardive dystonia are late onset syndromes that occur after prolonged treatment with antipsychotics. Table I outlines the important characteristics of these EPS variants.

A dystonia is a sustained posture produced by continuous muscular contraction. Acute dystonias are typically focal, affecting the muscles of the neck, jaw, back, extremities, eyes, throat and tongue. They are experienced by patients as extremely uncomfortable, if not outright painful. Most acute dystonias occur within the first week of treatment and sometimes within the first few hours after the initial antipsychotic dose,[14] especially with declining antipsychotic plasma concentrations. The risk of antipsychotic-induced dystonia is greatest in young men.[15]

Akathisia describes a subjective feeling of internal motor restlessness that usually occurs within several days to weeks of antipsychotic therapy at peak drug concentrations.[15] The restlessness is typically present throughout the body, but is sometimes confined to the legs. Akathisia is experienced by patients as highly disturbing and may be described as tension, nervousness or anxiety (without awareness that it is a drug-induced adverse effect). Objectively, the patient can often be observed rocking, pacing or generally unable to keep still. Clinicians may mistake akathisia for psychotic agitation, prompting an increase in antipsychotic administration and a consequent worsening (or prolongation) of the condition.

Antipsychotic-induced parkinsonism manifests in a similar way to Parkinson's disease, with the

Table I. Antipsychotic-induced movement disorders

Movement disorder	Description	Onset	Treatment	Rating scale
Akathisia	Subjective feeling of motoric restlessness	Hours to days	Propranolol Benzodiazepines	ESRS BAS
Dystonia	Sustained muscular contraction	Hours to days	Anticholinergics administered parenterally	ESRS SAS
Parkinsonism	Bradykinesia, rigidity, tremor	Weeks	Anticholinergics	ESRS
			Amantadine	SAS
Tardive dyskinesia	Late onset choreiform movements	3 months to years	Atypical antipsychotics	ESRS
			Tocopherol (vitamin E)	AIMS
Tardive dystonia	Late onset dystonias	3 months to years	Clozapine	ESRS SAS

AIMS = Abnormal Involuntary Rating Scale; **BAS** = Barnes Akathisia Scale; **ESRS** = Extrapyramidal Symptom Rating Scale; **SAS** = Simpson Angus Scale.

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classic triad of rigidity, bradykinesia and tremor, although usually the tremor is less pronounced. Other stigmata of parkinsonism include hypomimia (masked facies), shuffling gait, stooped posture, sialorrhoea, and seborrhoea. Antipsychotic-induced parkinsonism, like akathisia, usually occurs within the first few weeks of antipsychotic therapy.[15] The elderly are at substantially greater risk.

Tardive dyskinesia manifests as choreiform (repetitive, irregular, jerky, usually short amplitude) movements that occur after several months to years of antipsychotic therapy. The involuntary movements typically involve the muscles of the lower face (lips, jaw, tongue) and distal extremities. Classic movements include lip smacking, tongue protrusion, grimacing and 'piano (or guitar) playing' movements of the fingers or toes. The movements are increased by distraction and suppressed by action of and directed attention at the involved body part. Unlike acute EPS, tardive dyskinesia is usually first detected by family members or treating clinicians rather than patients, who are rarely aware of, or disturbed by, the movements. Risk factors include older age, female sex, diabetes mellitus, alcohol abuse, affective disorders and acute EPS.[16] Tardive dystonia describes the emergence of dystonic movements in a tardive fashion. Although tardive dystonia is often lumped into tardive dyskinesia, some have argued that it is a distinct entity with different clinical features.[17-19]

Examination of EPS can be performed easily by a clinician trained to recognise the various movements. Detection and quantification of these movement disorders is formally assessed in clinical trials using several different standardised rating scales such as the Barnes Akathisia Scale,[20] Simpson Angus Scale,[21] Abnormal Involuntary Movement Scale[22] and Extrapyramidal Symptom Rating Scale.[23]

2. EPS Associated With Atypical Antipsychotics

2.1 Clozapine

2.1.1 Acute EPS Associated with Clozapine

The approval of clozapine for use in the US, despite its prior removal from the European market because of agranulocytosis, was prompted by a landmark study published in 1988.[3] This trial compared clozapine with a low potency conventional antipsychotic, chlorpromazine, in the treatment of patients with refractory schizophrenia over 6 weeks. Chlorpromazine-treated patients were all given benzatropine to mitigate acute EPS and preserve the study blindness against clozapine. Despite this, clozapine-treated subjects had significantly less severe acute EPS than chlorpromazine-treated patients at the end of the study, although the severity of EPS in both treatment arms was fairly mild by study endpoint. The relative percentages of patients with EPS in each treatment arm were not reported. An earlier double-blind study in non-refractory patients compared clozapine with chlorpromazine for 4 weeks.[24] In this trial, acute EPS were again less prominent with clozapine treatment and study participants leaving the trial because of EPS were significantly fewer compared with chlorpromazine. Acute EPS (akathisia, dystonia, rigidity or tremor) were noted in 12% of clozapine- and 25% of chlorpromazine-treated subjects. Prophylactic anticholinergic use was not reported. Of note, in both of these studies, the Simpson Angus Scale was used to measure acute EPS and the score was calculated based on the total score minus the hypersalivation item, since clozapine produces sialorrhoea independent of extrapyramidal toxicity. In contrast, conventional antipsychotics typically cause hypersalivation because of bradykinesia (EPS) of the swallowing muscles. Based on a total of sixteen studies comparing clozapine to a conventional antipsychotic, a meta-analysis confirmed that acute EPS are indeed significantly less frequent with clozapine than with conventional antipsychotic comparators.[25]

2.1.2 Tardive Syndromes Associated with Clozapine

Tardive dyskinesia arising in the context of clozapine therapy has been reported in the case report literature[26-29] and in open-label studies;[30] however, because clozapine is reserved for refractory patients or those with severe tardive dyskinesia, the influence of prior antipsychotic exposure is invariably important as a potential causal factor. In fact, there is ample evidence that clozapine has a mitigating effect on antipsychotic-induced tardive dyskinesia. A number of open-label studies have demon-

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strated that tardive dyskinesia may improve upon switching to clozapine therapy,[31-36] as is also the case for tardive dystonia.[37-40] Additional reports have noted the emergence of tardive dyskinesia and tardive dystonia upon discontinuation or dose reduction of clozapine.[31,41-43] These data suggest that clozapine is not only associated with a low risk of tardive dyskinesia itself, but that it may have the ability to suppress tardive dyskinesia and especially tardive dystonia.

2.2 Risperidone

2.2.1 Acute EPS Associated with Risperidone

Risperidone was the first atypical antipsychotic to be approved and released following clozapine. It is a potent inhibitor of D_2 receptors, causing greater prolactin elevations than other atypical antipsychotics and even haloperidol.[44] The pivotal multicenter trial of risperidone was performed in North America and the dataset was divided and published in two separate papers.[45,46] The double-blind study compared four dosages of risperidone (2, 6, 10 and 16 mg/day) to haloperidol 20 mg/day and placebo over 8 weeks. Chounaird et al.[45] reported on the Canadian data and found that risperidone at a dosage of 10 mg/day, like haloperidol at a dosage of 20 mg/day, caused more parkinsonism than did placebo. A linear dose-response relationship was found for risperidone and parkinsonism. Looking at the number of subjects prescribed anticholinergic medication for acute EPS during the study, the percentage increased with the risperidone dose but was still comparable with placebo across all doses. Patients receiving risperidone 2, 6 and 10 mg/day were prescribed significantly less anticholinergic medication than haloperidol treated subjects. Marder and Meibach[46] reported on the US data and found similar results. Treatment with risperidone 2 and 6 mg/day resulted in EPS ratings that were comparable to placebo. Patients treated with risperidone 16 mg/day and haloperidol 20 mg/day had significantly more severe EPS and significantly more of these patients required anticholinergic medications than the placebo treated subjects. Simpson and Lindenmayer[47] examined the combined data from these trials and reported on more detailed assessments of EPS. They found that 1.7% of risperidone-treated subjects had dystonic reactions compared with 2.4% of haloperidol-treated subjects. For parkinsonism ratings, risperidone was no different than placebo at dosages of 2, 6 and 10 mg/day and caused significantly less parkinsonism than haloperidol across all doses. Likewise, haloperidol treated patients received significantly more anticholinergic medications than patients treated with risperidone at dosages of 2, 6 and 10 mg/day. The acute EPS risk for risperidone was clearly dose-related, although the high doses were still associated with less EPS than haloperidol. Risperidone 2 and 6 mg/day were comparable to placebo with regard to EPS prevalence and the amount of anticholinergic medications administered for acute EPS.

It could be argued that the choice of haloperidol 20 mg/day in the North American trial might have biased the results in favour of risperidone with respect to EPS. However, another large study comparing risperidone 1, 4, 8, 12 and 16 mg/day with haloperidol 10 mg/day still found significantly more parkinsonism with haloperidol than with any risperidone dosage except 16 mg/day.[48] Dystonia and akathisia were also significantly less severe with all risperidone doses compared with haloperidol. The percentage of patients requiring anticholinergic medications was significantly greater for haloperidol than for any risperidone doses. Therefore, risperidone still seems to cause fewer acute EPS compared with a more comparable mid-range haloperidol dose. The ideal study design to estimate the incidence of antipsychotic associated EPS would examine first-episode patients followed prospectively on a single agent, thereby avoiding pretreatment effects. Kopala et al.[49] performed such a study with risperidone and found that after treatment with risperidone 2–4 mg/day, there were no EPS. EPS (akathisia and parkinsonism) did emerge with risperidone at a dosage of 5–8 mg/day and these doses were found to be less efficacious for the control of positive and negative symptoms.

Taken together, the results of these trials suggest that when risperidone is dosed in the range of 4–6 mg/day (now considered to be the optimal dose range for risperidone efficacy),[50] the frequency of acute EPS are comparable to placebo and significantly less likely than with haloperidol therapy. However, risperidone can cause EPS in a dose-

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dependent fashion and this risk increases when the dosages are pushed beyond 6 mg/day.

2.2.2 Tardive Syndromes Associated with Risperidone

Both tardive dyskinesia and tardive dystonia have been reported with risperidone in patients previously treated with conventional antipsychotics[51-62] as well as in antipsychotic treatment-naive patients.[63,64] However, just as with clozapine, the case report literature also includes reports of patients whose tardive dyskinesia improved or resolved upon switching to risperidone therapy.[65-68]

Chouinard[69] reported on the incidence of tardive dyskinesia in the Canadian risperidone trial described in section 2.2.1 and found that treatment with risperidone at dosages of 6, 10 and 16 mg/day was associated with lower dyskinesia scores than treatment with either haloperidol or placebo. When patients with tardive dyskinesia (diagnosed with formal research criteria) were examined, risperidone again demonstrated an 'antidyskinetic' effect (i.e. dyskinesia scores improved) not seen with placebo or haloperidol. The lower rate of dyskinetic movements in patients receiving risperidone compared with placebo suggests that risperidone, like clozapine, may have the ability to suppress tardive dyskinesia.

The rates of treatment emergent tardive dyskinesia also seem to be low for risperidone. A meta-analysis of double-blind trials involving risperidone reported that only 0.22% of patients receiving risperidone for at least 12 weeks developed tardive dyskinesia.[70] In a long-term, double-blind study of up to a year, Csernansky et al.[71] followed patients receiving risperidone (mean modal dosage 4.9 mg/day) or haloperidol (mean modal dosage 11.7 mg/day) and detected new onset tardive dyskinesia in 0.6% of risperidone- and 2.7% of haloperidol-treated patients. Longer-term prospective studies specifically surveying for tardive dyskinesia in geriatric patients have confirmed a reduced risk of tardive dyskinesia associated with risperidone even in this at risk population. Jeste et al.[72] followed patients with a mean age of 66 years and a variety of different psychiatric diagnoses who were treated with risperidone and matched controls treated with haloperidol. The mean dosage for both medications was only 1 mg/day. The cumulative 9-month incidence of tardive dyskinesia was approximately 5% for risperidone-treated patients and 30% for haloperidol-treated patients. Furthermore, emergent tardive dyskinesia plateaued at 3 months for risperidone, although for haloperidol the tardive dyskinesia rate was still increasing linearly at 9 months. In a second study involving older patients (mean age 82.5 years) without tardive dyskinesia at baseline, Jeste et al.[73] found a 1-year cumulative tardive dyskinesia incidence of 2.6% for risperidone. Nearly 50% of subjects with dyskinesias at baseline experienced significant reductions in dyskinetic movements following risperidone treatment. These studies suggest that risperidone has a significantly lower 1-year risk of inducing tardive dyskinesia than haloperidol, even in elderly patients who are at particularly high risk.

2.3 Olanzapine

2.3.1 Acute EPS Associated with Olanzapine

Of all the available atypical antipsychotics, olanzapine bears the closest structural resemblance to clozapine. It also shares a high degree of *in vitro* antimuscarinic affinity with clozapine, raising the possibility that this might result in low extrapyramidal toxicity. Tran et al.[74] collectively analysed the results of three 6-week double-blind studies comparing olanzapine (mean dosage 12.8 mg/day) with haloperidol (mean dosage 12.7 mg/day) in >2500 subjects.[74] Acute EPS were determined by a variety of different outcome measures including reported adverse events, categorical EPS diagnoses, mean change in EPS rating scale scores and rates of anticholinergic administration. Based on reported adverse events, the authors found that significantly fewer subjects treated with olanzapine compared with haloperidol experienced dystonias (1.4% vs 6.3%), parkinsonism (9.4% vs 28.4%), akathisia (7.0% vs 21.5%) or 'any' form of EPS (18% vs 46.5%). Likewise, using research definitions of various EPS, significantly fewer olanzapine-treated patients compared with haloperidol-treated patients experienced parkinsonism (14.3% vs 39.8%), akathisia (13.0% vs 40.2%) or required anticholinergic medication (15.5% vs 47.0%). Quantified measures of EPS demonstrated that olanzapine-treated patients improved with regard to ratings of parkin-

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sonism and akathisia, whereas haloperidol-treated subjects had increases in the severity of these symptoms. Therefore, based on a variety of different outcomes to measure acute EPS, this large study demonstrated consistently significant advantages for olanzapine compared with haloperidol. Another open-label study reported on EPS rates upon switching haloperidol (mean dosage 12.7 mg/day) to olanzapine (mean dosage 11.4 mg/day).[75] Akathisia scores improved by 82%, parkinsonism scores improved by 87% and anticholinergic use declined significantly. These results confirm that switching from haloperidol to olanzapine can have beneficial effects on pre-existing EPS.

2.3.2 Tardive Syndromes Associated with Olanzapine

Case reports with olanzapine follow the familiar pattern of documenting both emergent tardive dyskinesia and tardive dystonia,[76-78] including a patient without prior antipsychotic exposure[79] as well as improvements in tardive dyskinesia and tardive dystonia.[80-92] The literature from controlled trials is consistent with a low risk of tardive dyskinesia associated with olanzapine relative to haloperidol therapy. Tollefson et al.[93] reported on three long-term maintenance studies comparing olanzapine with haloperidol, with mean dosages of 14.4 mg/day and 14.7 mg/day, respectively. Only subjects without a history of tardive dyskinesia and without the condition at study baseline were included in the analysis. Looking at three different research definitions of emergent tardive dyskinesia, the olanzapine-induced rate varied from 1.0% to 7.1%, whereas the haloperidol-induced rate varied from 4.6% to 16.2%. This difference was significant and reflects the rate of tardive dyskinesia over the course of several months of antipsychotic treatment. In an expanded analysis examining long-term double-blind studies with olanzapine, haloperidol and placebo, the overall 1-year risk of tardive dyskinesia was found to be 2.6% for olanzapine and 8.0% for haloperidol.[94] When subjects who responded to treatment and did not meet tardive dyskinesia criteria after the first 6 weeks of study were followed to endpoint (increasing the likelihood that subjects with withdrawal dyskinesias would be excluded), the 1-year tardive dyskinesia risks were 0.5% for olanzapine and 7.5% for haloperidol. These data reflect a tardive dyskinesia relative risk for olanzapine compared with haloperidol of 11.4.

2.4 Quetiapine

2.4.1 Acute EPS Associated with Quetiapine

Quetiapine was released in 1997 as the fourth atypical antipsychotic to come to the market in the US. Arvanitis and Miller[95] performed the major dose-finding trial for quetiapine (up to 750 mg/day) compared with haloperidol and placebo. In this study, EPS-related adverse events were reported in 6.2% of quetiapine-treated patients, 18% of placebo-treated patients and 37% of haloperidol-treated patients. The rates of specific movement disorders were dystonia (placebo 2%, quetiapine 0.8%, haloperidol 2%), parkinsonism (placebo 10%, quetiapine 5%, haloperidol 29%) and akathisia (placebo 8%, quetiapine 1.1%, haloperidol 15%). For change in mean EPS ratings, there were no differences between placebo, quetiapine or haloperidol. No dose-response relationship was found for quetiapine and EPS, suggesting that unlike risperidone, the antipsychotic threshold is not typically encountered within approved dose ranges for quetiapine.

Another study compared two dosage ranges (≤650 mg/day and ≤250 mg/day) of quetiapine with placebo, although the mean dosages (360 mg/day and 209 mg/day) were both in what would now be considered the low to medium range of quetiapine administration.[96] The rates of EPS change on either quetiapine doses were no different than placebo. Therefore, these studies indicate an extremely low EPS risk with quetiapine, leading some to speculate that the rapid dissociation of quetiapine from the D_2 receptor mediates this effect and therefore its (as well as clozapine's) 'atypical' nature.[97,98]

2.4.2 Tardive Syndromes Associated with Quetiapine

As with the other atypical antipsychotics, case reports with quetiapine have documented emergent tardive dyskinesia in patients with prior antipsychotic exposure,[99,100] as well as tardive dyskinesia improvement and resolution in patients changed to quetiapine therapy.[82,101-103] Controlled studies of tardive dyskinesia with quetiapine are lacking at this time, although the results of short-term studies have

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demonstrated effects on tardive dyskinesia scores comparable to placebo.[95,96]

2.5 Ziprasidone

2.5.1 Acute EPS and Tardive Syndromes Associated with Ziprasidone

Ziprasidone was released in 2001 in the US and has some interesting pharmacological properties including serotonin and noradrenaline (norepinephrine) reuptake inhibition (similar to the antidepressant venlafaxine) and serotonin 5-HT_{1A} inhibition (like the anxiolytic buspirone), in addition to D_2 antagonism. It not yet clear whether these added receptor activities will translate into meaningful clinical benefits. With regard to acute EPS, data from several short-term studies indicate a low risk comparable to that of placebo.[104-106] A longer-term study compared flexibly-dosed ziprasidone (80–160 mg/day, mean dosage 116 mg/day) with haloperidol (5–15 mg/day, mean dosage 8.6 mg/day) over 28 weeks.[107] Akathisia (ziprasidone 14%, haloperidol 16%), hypertonia (ziprasidone 2%, haloperidol 7%), tremor (ziprasidone 6%, haloperidol 10%) and 'extrapyramidal syndrome' (ziprasidone 1%, haloperidol 5%) were all reported less frequently with ziprasidone than with haloperidol. Although akathisia and parkinsonism ratings increased in the haloperidol group, parkinsonism ratings decreased for ziprasidone and akathisia scores remained unchanged with ziprasidone therapy. This is notable given that the choice of a comparator haloperidol dose was low relative to other trials.

At the time of this publication, there has been only one case report of tardive dyskinesia with ziprasidone.[108] A 28-week trial found a decrease in tardive dyskinesia ratings during ziprasidone treatment but an increase with haloperidol treatment.[107] Determining the rate of tardive dyskinesia with ziprasidone will require additional clinical research experience with this drug.

2.6 Aripiprazole

2.6.1 Acute EPS and Tardive Syndromes Associated with Aripiprazole

Aripiprazole is the latest atypical antipsychotic to be released to date. This new drug boasts a fairly novel mechanism of action in the antipsychotic armamentarium. Rather than being a pure antagonist at D_2 receptors like every other antipsychotic currently available in the US, it is a partial D_2 agonist. It has therefore been marketed as having less of a potential for D_2 antagonism in the nigrostriatal regions that give rise to EPS. The single published trial of aripiprazole for acute EPS compared aripiprazole to haloperidol and placebo in an 8-week study.[109] Aripiprazole was studied at dosages of 15 and 30 mg/day while haloperidol was administered at 10 mg/day. The reported EPS rates were akathisia (placebo 11%, aripiprazole 8–12%, haloperidol 23%), hypertonia (placebo 5%, aripiprazole 2–8%, haloperidol 3%), and tremor (placebo 3%, aripiprazole 2–3%, haloperidol 7%). Acute EPS rating scale score changes with aripiprazole were comparable to placebo.

Marder et al.[110] recently reported on five different 4–6-week phase II and III studies that compared aripiprazole with placebo and haloperidol. The overall rate of reported EPS-related adverse events for aripiprazole (21.1%) was comparable to that of placebo (19.4%), although the haloperidol rate was significantly higher (43.5%). Looking at changes in rated EPS, aripiprazole was comparable to placebo and EPS changes were unrelated to the aripiprazole dose. Only 18.7% of aripiprazole-treated patients required anticholinergic medications compared with 14.8% of placebo- and 42.0% of haloperidol-treated subjects. However, both aripiprazole at a dosage of 15 mg/day and haloperidol were associated with significantly greater worsening of akathisia than was found with placebo, although probably not to a clinically relevant degree.

There have been no reports of tardive dyskinesia associated with aripiprazole to date. Kane et al.[109] found mild decreases in mean tardive dyskinesia scores with aripiprazole in their short trial, though this was true of haloperidol as well. Marder et al.[110] reported significant improvements in tardive dyskinesia scores compared with placebo and a reported tardive dyskinesia rate of 0.2% during the short-term trials summarised in their review. Like ziprasidone, additional experience with this new drug is needed to better estimate the rate of tardive dyskinesia.

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Table II. Research definitions of tardive dyskinesia (TD)

Definition authors	Definition
Schooler and Kane[111]	AIMS performed at each visit. TD defined as (a) cumulative antipsychotic exposure of ≥3 months and (b) AIMS score of ≥3 on one or more body part, or a score of ≥2 on at least two body parts
Morgenstern and Glazer[112]	AIMS performed at beginning and end of each visit. TD defined as (a) total AIMS score ≥3 on both exams at two successive visits and (b) score of ≥2 on at least one anatomic AIMS item on both exams at the same two visits
Jeste et al.[73]	DMS (an ESRS dyskinesia subscale) performed at each visit. Baseline TD defined as ≥3 on at least one item or ≥2 on at least two items of the DMS. Emergent TD defined as an increase from baseline of 3 points on one item or >2 points on two items of the DMS. Emergent persistent TD defined as emergent TD present on two consecutive visits

AIMS = Abnormal Involuntary Rating Scale; **DMS** = Dyskinetic Movement Scale; **ESRS** = Extrapyramidal Symptom Rating Scale.

3. Methodological Issues

3.1 Factors Related to Measurement and Diagnosis of EPS

EPS can be measured and defined using a variety of different methods. For example, several of the studies mentioned previously describe data on reported adverse events that fall into various EPS categories (i.e. akathisia, tremor, hypertonia or the generic 'extrapyramidal syndrome'). Although this is a common method of assessing adverse effects in clinical trials, it leaves EPS subject to misdiagnosis and underdetection. For example, a restless patient might have akathisia, but it might instead be reported as 'anxiety' or 'agitation'. In the case of tardive dyskinesia, a patient might not report it because they are subjectively unaware of the adverse effect or might have already experienced it for years. Likewise, clinicians and others administering rating scales not specifically designed to measure tardive dyskinesia might not recognise it in routine clinical assessment.

In order to enhance the characterisation and quantification of movement disorders, a variety of rating scales have been developed. Although these scales have been standardised and validated, the same scales are not always used from study to study. For example, some trials employ the Barnes Akathisia Scale,[20] Simpson Angus Scale[21] and Abnormal Involuntary Movement Scale[22] to measure akathisia, parkinsonism and tardive dyskinesia, respectively, while others use the Extrapyramidal Symptom Rating Scale[23] to measure dystonia, akathisia, parkinsonism, and tardive dyskinesia. These scales differ with regard to individual items and, therefore, may result in different severity ratings depending on the particular scale used. Of note, these scales are intended to quantify the severity of movement disorders and are not diagnostic tools. In order to address the categorical presence of absence of a movement disorder, several different research definitions have been formulated.[73,111,112] Table II summarises three different research definitions of tardive dyskinesia. Even subtle differences between tardive dyskinesia definitions could result in differences in whether a particular movement disorder is diagnosed. In addition, some studies have required the presence of tardive dyskinesia on two consecutive ratings; this more stringent definition would be expected to decrease the incidence of tardive dyskinesia. For example, in the study by Tollefson et al.,[93] the rate of tardive dyskinesia with olanzapine was reduced by half when two consecutive ratings were required for diagnosis. These various factors relating to detection and diagnosis make it difficult to reliably compare the incidence of EPS from one drug (or one study) to another.

3.2 Differential Diagnosis of Atypical Antipsychotic-Induced Tardive Dyskinesia

According to research definitions, tardive dyskinesia generally requires a minimum of 3 months of antipsychotic exposure to develop.[111] Once present, it typically waxes and wanes rather than following a deteriorating course or completely remitting. This fluctuating pattern means that within the confines of a short-term drug trial, patients with tardive dyskinesia may experience the worsening or improvement of tardive dyskinesia measures regardless of pharmacological intervention. Therefore, the changes in tardive dyskinesia ratings detected dur-

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ing such a study may or may not reflect changes related to antipsychotic treatment *per se*.

Spontaneous dyskinesias and withdrawal dyskinesias can also confound tardive dyskinesia monitoring during a short-term drug trial. Spontaneous dyskinesias can closely resemble tardive dyskinesia, but were observed in patients with schizophrenia long before the discovery of antipsychotic medications. The reported rate of such dyskinesias has been as high as 53%.[113] The development of dyskinesias can also be associated with normal aging, such that 4–8% of healthy elderly men will experience them.[113,114] Withdrawal dyskinesia describes the phenomenon in which tardive dyskinesia acutely worsens upon discontinuation of antipsychotic therapy. Clinical trials typically include a wash-out period prior to study commencement, but because of ethical issues it rarely lasts long enough to avoid the effects of prior antipsychotic treatment or the emergence of withdrawal dyskinesia. To complicate matters further, tardive dyskinesia has been reported with a variety of non-antipsychotic medications, including tricyclic and serotonergic antidepressants,[115-117] cocaine,[118] lithium,[119] oral contraceptives[119] and anticonvulsants.[119] Together these various non-antipsychotic induced dyskinesias can make it difficult to determine whether changes in tardive dyskinesia ratings during a short-term study are because of the initiation of a new drug, the lingering effects or withdrawal of prior treatment or other causes of dyskinesia. For these reasons, prospective longitudinal studies of tardive dyskinesia are preferred whereas cross-sectional point prevalence analyses reporting between drug differences must be interpreted cautiously. In addition, the use of both a placebo and active control is required to assess for withdrawal dyskinesias (which should manifest on placebo) and determine between-antipsychotic treatment effects.

3.3 Between-Drug Comparisons and Dose Issues

Several studies have examined large samples of patients in order to determine whether there is indeed a significant difference between conventional antipsychotics and atypical antipsychotics with regard to acute EPS. A point prevalence study reported that the rate of EPS was 78.3% for haloperidol, 55.1% for risperidone, 39.5% for quetiapine and 36.8% for olanzapine.[120] These overall differences were significant between haloperidol and the atypical antipsychotics and between risperidone and olanzapine. Risperidone was also associated with more rigidity, tremor and akathisia than olanzapine. However, this study was limited by its cross-sectional design and non-randomised treatment conditions. Another large study examined the rate of first-time antiparkinsonian medication prescriptions in new users of risperidone, olanzapine, and haloperidol. It found that patients treated with risperidone and olanzapine required fewer interventions for EPS than haloperidol-treated patients.[121] It also found that more patients treated with risperidone and olanzapine had a history of previously taking a conventional antipsychotic along with an antiparkinsonian medication, which highlighted the frequent potential for prior treatment effects in atypical antipsychotic users.

Three meta-analyses have also been performed to address the question of conventional antipsychotic/atypical antipsychotic differences in the incidence of EPS. The first study examined 19 trials comparing risperidone, olanzapine or quetiapine with haloperidol and found that each of the atypical antipsychotics were superior to haloperidol on the outcome of use of antiparkinsonian medication, with large effect sizes.[122] Another larger study analysed the results of 52 trials involving a variety of conventional antipsychotics (usually haloperidol or chlorpromazine) and atypical antipsychotics (including clozapine, risperidone, olanzapine and quetiapine) and found no differences in antipsychotic efficacy between the atypical and conventional antipsychotics dosed at ≤12 mg/day haloperidol equivalents.[12] However, the atypical antipsychotics still had a modest advantage in terms of EPS, even when the dose was controlled for. A third meta-analysis, recognising that the use of haloperidol as a comparator might bias EPS results in favour of atypical antipsychotics, analysed 31 studies comparing atypical antipsychotics to low-potency conventional antipsychotics.[13] This study concluded that only clozapine produced significantly fewer EPS than the conventional antipsychotics. Olanzapine had an advantage at the trend level, while risperidone and quetiapine, partly because of a dearth of studies

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comparing them to low potency conventional antipsychotics, were found to be no better. When studies that involved only low potency conventional antipsychotic dosages of ≤600 mg/day chlorpromazine equivalents were considered, no atypical antipsychotics were superior with regard to EPS. When these meta-analyses are considered, together with the short-term trials discussed previously, it becomes clear that atypical antipsychotics do offer a significant EPS advantage over conventional antipsychotics. However, this advantage diminishes when atypical antipsychotics are compared with low-potency conventional antipsychotics and lower doses of high potency conventional antipsychotics.

A fourth, recently published, meta-analysis examined tardive dyskinesia rates with novel antipsychotic medications.[123] This study included 11 trials of ≥1-year duration involving risperidone, olanzapine, quetiapine, amisulpiride and ziprasidone in which tardive dyskinesia was formally assessed at regular intervals. The weighted mean annual incidence risk of tardive dyskinesia that is associated with these novel antipsychotic medications across all age groups was 2.1%. For adults (children and elderly excluded), the mean annual incidence risk was 0.8%. The corresponding risk for haloperidol in adults, based on three studies involving a haloperidol control arm, was 5.4%, although all three studies utilised a mean haloperidol dosage of >10 mg/day. This study, therefore, suggests a 5-fold lower risk of tardive dyskinesia for the novel medications compared with haloperidol.

The comparison of between-atypical antipsychotic differences in EPS and tardive dyskinesia incidence has been less well studied. The ideal study design to address this issue would involve first-episode patients without previous antipsychotic treatment followed over several years of therapy with different atypical antipsychotics. No such trials exist. Most existing studies involve the comparison of an atypical antipsychotic to risperidone, which is the most likely atypical agent to cause EPS at a standard dose. The results of these head to head trials have been heavily influenced by the dose of risperidone studied. For example, in one study comparing olanzapine to a mean dosage of risperidone of 4.8 mg/day, no differences in the rates of EPS were detected as measured by the Extrapyramidal Symptom Rating Scale.[124] However, another study that compared olanzapine with a mean risperidone dosage of 7.2 mg/day found significantly fewer EPS in the olanzapine-treated group.[125] Klieser et al.[126] compared clozapine to two dosages of risperidone (2 and 4 mg/day) and reported no differences in acute EPS between treatment groups. A fourth trial compared quetiapine (mean dosage 254 mg/day) to risperidone (mean dosage 4.4 mg/day) and found significantly fewer EPS interventions (dose reduction and anticholinergic administration) with quetiapine.[127]

At present, the between-atypical antipsychotic rates of EPS cannot be reliably estimated because of a lack of well-designed studies and other methodological issues, although the available evidence does indicate that risperidone carries the greatest risk of EPS, particularly at dosages of >4–6 mg/day.

4. Therapeutic Interventions

4.1 Preventative Strategies

The rationale for using atypical antipsychotics as first line therapy in the US is based largely on their reduced risk of inducing acute EPS and tardive dyskinesia. The use of atypical antipsychotics in lieu of conventional antipsychotics, therefore, is a primary preventative strategy for EPS. The safest and most effective preventative strategy involves not prescribing antipsychotic medications at all to individuals for whom they are not required. At present, the atypical antipsychotics are being used for increasingly diverse off-label uses (insomnia, anxiety disorders, depression, etc.) despite a lack of efficacy data from rigorous controlled studies. Although the atypical antipsychotics do have a lower EPS risk and are clearly better tolerated than the conventional antipsychotics, they still have the potential for serious adverse effects and should be prescribed judiciously.

If a patient does require treatment with an antipsychotic medication, then limiting the dose and duration of therapy is generally recommended. However, studies involving conventional antipsychotics have revealed that drug holidays are ineffective at reducing tardive dyskinesia and may in fact increase the tardive dyskinesia risk.[128,129] With respect to

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dose, acute EPS are clearly dose related and data involving conventional antipsychotics indicate that once an agent is dosed past the antipsychotic threshold, it is unlikely to be more effective (and may instead be less effective) than lower doses.[130-132] With the exception of risperidone, the antipsychotic threshold should not typically be encountered within standard dose ranges of atypical antipsychotic therapy. Therefore, where the antipsychotic threshold lies with these new medications and whether pushing doses beyond the approved ranges might be effective for some refractory patients is not yet clear. Despite the lack of empirical data, high-dose therapy with the atypical antipsychotics is on the rise in clinical practice.[133] This practice may increase the overall rate of acute EPS while creating, in effect, a very expensive conventional antipsychotic out of an 'atypical' antipsychotic medication. Since the majority of patients being treated with atypical antipsychotics should not experience acute EPS during standard administration, it follows that avoiding high-dose therapy would be useful in preventing acute EPS. Although it is logical based on acute EPS being a risk factor for tardive dyskinesia, it does not necessarily follow that high-dose atypical antipsychotic therapy will put patients at greater risk for tardive dyskinesia. In the case of the conventional antipsychotics, a higher dose has not been firmly established as increasing the risk of tardive dyskinesia.[134]

Aside from limiting antipsychotic exposure to prevent tardive dyskinesia, another potential intervention lies in the use of adjunctive agents to decrease the risk of emergent tardive dyskinesia. To date, the most popular preventative strategy has included tocopherol (vitamin E) supplementation. The choice of tocopherol is based on the theory that tardive dyskinesia may be caused by oxidative damage secondary to excessive dopamine turnover in the brain. Tocopherol acts as a free radical scavenger and antioxidant, thereby potentially limiting neurodegeneration. While this is an inviting hypothesis, there have been no trials specifically designed to determine whether tocopherol may prevent tardive dyskinesia. Instead, existing tocopherol trials involve patients who already have tardive dyskinesia at baseline. However, a recent meta-analysis of these studies did find that tocopherol-treated patients had less worsening of tardive dyskinesia than patients treated with placebo.[135] At present, there is not yet sufficient evidence to support the efficacy of tocopherol as a prophylactic strategy for tardive dyskinesia. On the other hand, it appears to be a fairly innocuous intervention, with increasing evidence that it may be beneficial in the prophylaxis of cognitive decline in the elderly.[136]

4.2 Treatments for Acute EPS

For 40 years, the mainstay of management of acute EPS with conventional antipsychotics has included the use of anticholinergic medications, often in a prophylactic fashion. For acute dystonias, intramuscular medications such as benzatropine or diphenhydramine are preferred, although the clinician must remember that the half-life of antipsychotic medications often exceeds that of anticholinergic antidotes, such that additional doses may be required. Parkinsonism usually calls for standing doses of oral anticholinergic medication, although this can be of limited utility.[15] For akathisia, β-adrenoceptor antagonists (β-blockers) such as propranolol are the treatment of choice.[137] With the atypical antipsychotics, in most cases, the use of anticholinergic medications should not be necessary. On the contrary, the available evidence suggests that if acute EPS are encountered with atypical antipsychotic therapy, a decrease in dose is probably indicated.

4.3 Treatments for Tardive Syndromes

Given the lower risk of tardive dyskinesia with atypical antipsychotics, a trial of these agents is indicated for patients maintained on conventional antipsychotics who experience tardive dyskinesia, although the potential loss of antipsychotic efficacy is a risk. It could also be argued that in the setting of tardive dystonia, a clozapine trial is warranted based on its reported preferential efficacy for this syndrome.[17,18] The failure to recognise tardive dyskinesia or switch a patient to an atypical antipsychotic to address it could constitute malpractice.[10,11] Accordingly, any patient treated with antipsychotic medications should be monitored on a regular basis for tardive dyskinesia, bearing in mind

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that it may begin insidiously and require careful examination to detect.

A variety of different adjunctive medication strategies have been examined for the treatment of tardive dyskinesia, although generally speaking, definitive studies are still lacking. The efficacy of such interventions has been discussed in a recent review paper[134] and a meta-analysis based on the Cochrane Collaboration.[138] In the case of dopaminergic drugs, dopamine depleters (reserpine, tetrabenazine, alpha-methyl-para-tyrosine) seem to be effective in approximately 50% of patients with tardive dyskinesia but can cause acute EPS and have other difficult-to-tolerate adverse effects.[134] Double-blind studies involving dopamine agonists have been largely negative,[134] although levodopa was found to be effective in the Cochrane meta-analysis based on three small studies.[138] However, pro-dopaminergic drugs are often difficult to tolerate because of nausea and have the potential to exacerbate psychosis. Anticholinergics, which form the mainstay of acute EPS therapy, seem to have little benefit in reducing tardive dyskinesia and can worsen it.[128,139] In fact, anticholinergic discontinuation may be more useful in terms of improving tardive dyskinesia, although acute EPS could emerge as a result. High-dose anticholinergic therapy with trihexyphenidyl has been reported to be effective for tardive dystonia,[19,134] which suggests that the efficacy of clozapine might be due, at least in part, to its strong anticholinergic properties. GABA receptor agonists have shown promise in the treatment of tardive dyskinesia, with 43% of double-blind studies involving benzodiazepines yielding improvements in the condition[134] and the Cochrane meta-analysis finding favourable results with valproic acid (sodium valproate) based on two small studies.[138] Taken together, these various results raise the possibility that some adjunctive strategies might be useful, although larger, more rigorously designed studies are needed to address their efficacy with greater certainty. In addition, the currently available evidence suggests that the benefit-risk ratios of these treatments are not favourable enough to make them worthwhile interventions in the majority of cases.

Tocopherol has been the most studied pharmacological intervention for tardive dyskinesia, with 16 double-blind, placebo-controlled trials comparing the vitamin at a dosage of 1200–1600 mg/day with placebo in patients with tardive dyskinesia receiving antipsychotic therapy. These trials have all been relatively small, including <40 patients in each study, but are strengthened by a placebo control and in many cases a crossover design, allowing for within (rather than between) subject comparisons. For the most part, the studies have found positive benefits with tocopherol at a dosage of 1200–1600 mg/day compared with placebo,[84,140-146] particularly for patients with tardive dyskinesia of <5 years' duration.[147-149] The finding that longstanding tardive dyskinesia might be less responsive to antioxidant therapy is consistent with the hypothesis that tocopherol acts by preventing neurodegeneration due to oxidative injury. According to this view, antioxidants should halt or slow the development of tardive dyskinesia rather than reverse it. Although these study results are encouraging, the degree of improvement reported has been fairly modest, ranging from a 24% to 43% change in tardive dyskinesia ratings. In addition, in most cases the study duration has been relatively brief, limited to just a few weeks.

In contrast to the studies discussed previously, several tocopherol trials have failed to demonstrate a benefit for this intervention. Five small crossover trials yielded negative results,[147,150-152] although one may have been too brief to detect an effect at only 2 weeks' duration.[153] The largest and longest double-blind study of tocopherol for tardive dyskinesia conducted to date was a multicenter trial involving 158 subjects, who were followed for 1 year.[154] This trial included patients who had tardive dyskinesia based on two consecutive ratings and included electromechanical measures of dyskinesia. In order to select for patients with a potential treatment response based on the studies described earlier in this section, subjects with tardive dyskinesia of more than 10 years' duration were excluded. For the approximately 70% of subjects who completed a year in the study, no significant differences were found for any measures of acute EPS or tardive dyskinesia between the tocopherol and placebo groups. The investigators, who participated in several of the previously described pilot trials, postulate that their negative findings might be attributable to population differences. For example, 36% of patients in their study were receiving treatment with

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risperidone or olanzapine, whereas most of the prior studies were performed before the release of the atypical antipsychotics. In addition, patients could have their antipsychotic medications switched over the course of the study. The authors noted that because of the increase in atypical antipsychotic-prescribing practices, a selection bias may have resulted in studying patients with more refractory tardive dyskinesia, since those whose tardive dyskinesia would have resolved with a change to atypical antipsychotic therapy (or a reduction in conventional antipsychotic dose) would not have been included. In addition, many of the subjects had their anticholinergic medication discontinued during the study, which may have had a therapeutic effect (although more tocopherol-treated patients had anticholinergics withdrawn). Although these explanations may be valid, the cohort studied more closely matches current population characteristics, such that tocopherol may have a diminishing therapeutic role as atypical antipsychotic use continues to increase.

In summary, there are a handful of smaller trials, most (but not all) of which suggest that tocopherol may be of some benefit, and a larger, longer, more rigorously performed study demonstrating no benefit associated with tocopherol at 1-year follow-up. In order to examine the results of tocopherol studies as a whole, several meta-analyses have been performed. Prior to the large trial discussed, the results of which were published in 1999, these meta-analyses concluded that tocopherol did provide a modest benefit compared with placebo for the treatment of tardive dyskinesia.[155,156] However, the most recent meta-analysis that included the large, negative, multicenter study did not find sufficient evidence to conclude that tocopherol improves tardive dyskinesia.[135] Therefore, tocopherol therapy overall does not seem to have a benefit for tardive dyskinesia, although it may be of value in some subpopulations, such as individuals with mild recent-onset tardive dyskinesia who are still being treated with conventional antipsychotics. As noted earlier, tocopherol at a dosage of up to 1600 mg/day is fairly well tolerated and carries a low risk of any serious adverse effects.

Several other antioxidant compounds have been studied in the treatment of tardive dyskinesia. Selegiline and coenzyme Q have not been found to be effective.[134,157,158] On the other hand, a small 6-week crossover trial of melatonin 10 mg/day was found to decrease tardive dyskinesia ratings by 24%, which was significantly more than the placebo.[159] The authors state that melatonin is up to ten times more effective as an antioxidant than tocopherol and that it also enhances expression of a neurotrophic growth factor that acts on dopaminergic neurons. As with tocopherol, this new strategy will require further study in order to replicate its preliminary benefits.

5. Conclusion

The atypical antipsychotics have now replaced conventional antipsychotics as first-line therapy in the US because of their decreased risk of acute EPS and expectations that they will also, in the long run, cause less tardive dyskinesia. The available evidence presented in this review supports the notion that atypical antipsychotics are indeed safer with regard to extrapyramidal toxicity. The mechanism that underlies this 'atypicality' is currently being debated. Some have suggested that the reduced EPS risk is mediated by the pharmacodynamic characteristics of atypical antipsychotics, such as a higher potency for serotonin 5-HT_2 receptors relative to D_2 antagonism.[160] Others have theorised that the difference is primarily pharmacokinetic, based on atypical antipsychotics being less tightly and more transiently bound to the D_2 receptor than conventional antipsychotics.[98]

The use of atypical antipsychotics as first-line therapy is justified by the morbidity endured by patients treated with these medications who do experience acute EPS and tardive dyskinesia. Current research is also directed at determining whether atypical antipsychotics may also offer significant advantages in treating negative symptoms (although this is probably because of a reduction in negative symptoms secondary to EPS) and cognitive impairments in schizophrenia. Although atypical antipsychotics offer clear benefits, several important caveats are noted. First, the risk of EPS with atypical antipsychotics, although less than conventional antipsychotics, is not zero. Some of the superiority of atypical antipsychotics compared with conventional antipsychotics is biased by the use of inappropriately high doses of conventional antipsychotics such as

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haloperidol. At the same time, the doses of atypical antipsychotics used in clinical practice are increasing (with the exception of risperidone), which suggests that the EPS advantage of these agents could narrow as high-dose therapy becomes more frequent. Second, there are a host of other adverse effects now being investigated with atypical antipsychotics (weight gain, diabetes, cardiac effects and sexual adverse effects – the so called 'EPS of the new millennium') that may ultimately be more important than EPS with regard to morbidity and mortality.[161] Therefore, although the atypical antipsychotics offer valued benefits for patients with schizophrenia and other psychotic disorders, there is still room for much improvement in the development of more effective and safer antipsychotic medications.

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