



# Motor side effects of atypical antipsychotic drugs

The development of clozapine was thought to herald a new era of antipsychotic drug treatment by virtue of increased efficacy and fewer motor side effects. However, its non-motor side effects undermined its utility. We will argue that with the exception of quetiapine and clozapine, the other members of the 'atypical antipsychotics' have significant motor side effects, and that these side effects differ from drug to drug. All of the other compounds cause parkinsonism and worsen motor function in people with parkinsonian syndromes. Some are more likely than others to cause either acute dystonic reactions or akathisia. Only risperidone has so far been clearly linked as a cause of tardive dyskinesia when used long-term in neuroleptic-naïve patients, but this lack of association may be due only to limitations in data collection. All of the atypical antipsychotics, including quetiapine and clozapine, have been convincingly reported to cause neuroleptic malignant syndrome.

**KEYWORDS:** acute dystonic reaction ■ acute motor side effects ■ akathisia ■ atypical antipsychotic drugs ■ drug adverse effects ■ neuroleptic malignant syndrome ■ parkinsonism ■ tardive dyskinesia

There are two central issues to consider in assessing the motor side effects of atypical antipsychotic (AA) drugs. The first is the definition of what it means to be an AA drug. While one review states that 'the defining characteristic of an AA is its lower risk of inducing EPS [extrapyramidal symptoms] [1]' there is, in fact, no consensus definition [2] of what it means to be 'atypical'. All antipsychotics approved by the US FDA since clozapine in 1991 have been considered AA by the psychiatric community, despite the fact that there are no guidelines for using this designation. Clozapine is the only drug listed as an AA by the US FDA [3], with the later antipsychotics listed only by their chemical families. While several definitions for AAs have been proposed [2,4,5], the one most commonly considered in the medical community is 'relative freedom from extrapyramidal side effects', but what 'relative' means may be primarily in the minds of the marketing division of a drug company. The other criteria include:

- Pharmacological criteria based on relative dopamine to serotonin receptor blockade;
- Better improvement in negative symptoms of schizophrenia than the first generation of antipsychotic drugs;
- Lack of catalepsy in animal models when given doses thought to be proportionate to antipsychotic doses in humans;
- Mild and transient prolactin increases.

Some have labeled the antipsychotic drugs the 'second generation', in contrast to the drugs developed prior to clozapine. The problem with this designation is that clozapine, which was the first developed, is more atypical than the newer second-generation drugs. In addition, large studies performed by recognized experts have found less distinction from the first generation than anticipated [6].

The second issue lies in the inherent problems of recognizing motor side effects. This problem also has two components. For one thing there is some question about recognition of the motor effects [7-9]. In the era before the AAs, psychiatry residents were schooled in the recognition of the various drug-induced movement disorders, but even then [7], these were often missed. In the post-atypical era there is considerably less education in recognition of these disorders, making it more likely for them to go unrecognized [10].

However, more important are the problems inherent in the design of virtually every large antipsychotic drug trial. There are very few double-blind placebo-controlled trials or double-blind head-to-head trials of any antipsychotic drug for treatment-naïve subjects for obvious reasons. Reports on neuroleptic-naïve subjects are small in size, and therefore provide limited data on acute motor side effects and no data on tardive syndromes. The central problem in assessing motor side effects in the large, double-blind trials lies in the fact that the subjects had

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all been taking antipsychotics prior to enrollment and had gone through a washout period limited to 2 weeks or less. Since the motor side effects of parkinsonism may last for several months, this is clearly inadequate, and the emergence of tardive syndromes, which would show up as a treatment side effect, may actually indicate that the drug is less likely to mask a tardive syndrome and therefore more likely to be free of motor side effects. This apparent paradox is due to the fact that the dopamine D2-blocking drugs, which cause the movement disorders in the first place, can, at higher doses, mask some of the tardive syndromes. Therefore, the greater the side-effect profile, the better the side-effect profile of the drug might appear in a typical drug study. To exemplify this we can consider a trial of a drug or placebo that has no motor effects. A population of subjects who had been receiving haloperidol would undergo a washout period of 2 weeks. During this time, their parkinsonism may improve to some degree, while their tardive dyskinesic syndromes, often masked by the haloperidol, might be unmasked slightly. With time on a drug that has no motor effects, we would expect parkinsonism to improve and tardive dyskinesia (TD) to worsen. This drug, free of motor side effects, would be found in the study to worsen TD, and therefore to have significant motor side effects. On the other hand, if the subjects were placed back on haloperidol after a 2-week washout period, we would expect the TD to improve and the parkinsonism to return to baseline, and hence cause little or no motor side effects. Another example is a study on akathisia in which 29 people treated with clozapine as their only antipsychotic for at least 4 weeks were evaluated, of whom two (6.8%) had akathisia [11] – one of whom also had mild TD. Aside from the small numbers, the possibility of a tardive akathisia confounds interpretation of the report. In a large naturalistic study of TD by deLeon, ‘no significant effect comparing those taking only atypicals to those exposed to typicals for less than 5 years’ was found in the incidence of TD, but this report combined four atypicals into a single group [12].

As we will discuss below, one can obtain better insight into some of the drug side effects by reviewing their effects on people with Parkinson’s disease (PD). All the AAs have been tested in treating drug-induced psychosis, a common problem in PD, and this group is exquisitely sensitive to the motor side effects of the dopaminergic-blocking drugs, even at low doses. They function as the ‘canary in the mine

shaft’ to warn us of what a sensitive patient may experience, or what higher than average doses may do.

We will review each drug separately. We will not comment on their efficacy or their indications, but only their motor side effects.

### Potential motor side effects

There are several different potential motor side effects of these drugs which can be classified by their time of onset.

#### ■ Acute-onset movement disorders

Acute-onset movement disorders include acute dystonic reactions, akathisia and neuroleptic malignant syndrome [201]. These usually occur within the first few days of initiating or increasing the dosage of a drug. Acute dystonic reactions refer to recurrent paroxysmal episodes of sudden onset in which sustained muscle contractions cause abnormal involuntary postures lasting approximately 20–30 min. These usually involve muscles above the shoulders, with jaw clenching, tongue protrusion, torticollis and oculogyric crises (upward tonic gaze deviation usually associated with neck extension) being most common. They may also involve lower body segments, and look like tonic seizures. There is no impairment of consciousness. These are more common in the young, and in males, whereas akathisia and neuroleptic malignant syndrome do not have a clear epidemiology. Acute akathisia is a syndrome of uncomfortable restlessness which, when mild, may be perceived as extreme anxiety, relieved to some extent by constant movement. These patients fidget, walk about, march in place and cannot remain still. Unlike restless legs syndrome, there is no diurnal variation or paresthesiae in the legs. There is no gender or age predilection. Neuroleptic malignant syndrome is a life-threatening condition which is variably defined, but usually requires fever (often extremely high), severe extrapyramidal signs (usually profound rigidity) and altered mentation (usually stupor with delirium) [13].

#### ■ Parkinsonism

Parkinsonism usually develops over weeks and is more likely in the elderly [202], with females being more sensitive. In many cases, however, patients who have tolerated a drug for decades begin to show signs of parkinsonism despite there being no change in the antipsychotic drug regimen, raising the question of increased drug sensitivity after decades of exposure or the development of idiopathic PD.

### ■ Tardive syndromes

The tardive syndromes develop after long-term exposure to an antipsychotic, defined as greater than 1 month in someone over the age of 60 years or greater than 3 months in someone under that age. TD (Diagnostic and Statistical Manual of Mental Disorders [DSM IV-TR]) is more common in the elderly. Although the term TD is often used to describe the most common form of the syndrome, the classic oral–buccal–lingual dyskinesias, in which patients appear to be chewing and using their tongue to push food or candy around in their mouth although their mouths are empty, it really refers to a group of syndromes, with the choreic syndrome being by far the most frequent (Box 1). Some authorities use the term ‘tardive’ to mean persistent or long-lasting drug-induced movement disorders, but that is not the generally accepted definition.

### Atypical antipsychotic drugs

#### ■ Risperidone

Risperidone was approved for treatment of schizophrenia in 1993 [203]. Animal studies demonstrated that it had similarly high binding affinity to dopamine D2 receptors as haloperidol [14]; however, its serotonin receptor antagonist action was thought to impart some protection against developing parkinsonism and other movement disorders. Some of the early clinical studies stated that its propensity for causing extrapyramidal side effects was no greater than placebo [15], but with increased use, more cases appeared that proved this conclusion to be incorrect. While AAs have been shown in epidemiological studies to be less likely to induce a variety of drug-induced movement disorders [16], they do so at differing degrees with each syndrome [7]. The ‘atypicality’ of risperidone has been claimed for low doses only [17], as only low doses selectively bind outside the striatum, the motor aspect of the dopamine system.

#### Box 1. Drug-induced movement disorders.

- Acute dystonic reaction
- Acute akathisia
- Neuroleptic malignant syndrome
- Parkinsonism
- Tardive syndromes
- Oral–buccal–lingual dyskinesias
- Other choreic movements
- Akathisia
- Dystonia
- Pain
- Tics

Unfortunately, higher doses are frequently required, which are not selective. In addition, there is a large degree of biological variation in susceptibility to EPS of all types.

The reports on the movement side effects of risperidone are conflicting, and therefore difficult to interpret. In one study, the occurrence of drug-induced parkinsonism was found to be 42% compared with 29% with haloperidol [18], but the recent Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) report [6] found no differences in parkinsonism or any of the other movement side effects, as compared with perphenazine, although there was a significantly increased use of antiparkinson medications in the risperidone group alone. Risperidone has been reported to cause more parkinsonism than all other commercially available AAs in the USA [19,20]. In one study in which neuroleptic-naive psychotic patients were treated with either risperidone or haloperidol, open label, there were no significant differences between the drugs in terms of acute dystonic reactions, akathisia or parkinsonism [19].

An early study comparing risperidone and haloperidol, using doses of risperidone of up to 16 mg/day, which are rarely used these days, found that six of 344 subjects had acute dystonic reactions, and no change in TD or parkinsonism compared with placebo [21]. A recent study [22] compared the use of anticholinergics in a single blind study of patients who had had either acute dystonic reactions or parkinsonism on other antipsychotics, and found that a significant difference (odds ratio of 5:1) favored olanzapine as the drug with fewer motor side effects. A similar study compared risperidone to haloperidol [23]. An open-label trial of low-dose haloperidol, risperidone and olanzapine in neuroleptic-naive patients found that haloperidol-treated patients required more anticholinergics than either risperidone or olanzapine [24].

Tardive syndromes are thought to be less common with risperidone than with the first generation of antipsychotics, but the CATIE trial does not support this. Jeste *et al.* reported a rate of only 2.6% per year in elderly demented, a rate much lower than expected based on historical controls [25], as the elderly, particularly elderly with brain disorders, are thought to be the most likely to develop TD, yet there are a number of reports that indicate risperidone may induce tardive syndromes as readily as typicals [26–29]. At the other end of the age spectrum, a 1-year follow-up of risperidone-treated children, with a mean age of 9¼ years, reported only two new

cases of TD in 655 children. Other measures of drug-induced movement disorders did not change, and several children with TD at entry into the trial experienced improvement in their TD scores [30]. Reports of neuroleptic malignant syndrome (NMS) began appearing in the literature 2 years after its approval in both the adult and pediatric populations. The frequency of occurrence of NMS caused by typical antipsychotics varies from 0.02 to 2.44% in the literature, and it is thought that atypical agents have a lower frequency in comparison.

If one looks at the limited literature on the effects of risperidone on people with idiopathic PD who were treated with low doses of the drug, a marked discrepancy is seen, with some reports having no adverse motor outcomes and others [31,32] reporting 11 of 12 patients being intolerant due to motor decline.

#### ■ Olanzapine

Olanzapine is a thienobenzodiazepine introduced for clinical use in 1996 for schizophrenia [203]. While similar in structure to clozapine, olanzapine has a much higher propensity to worsen parkinsonism in PD patients [33], but less so than risperidone [7].

There have only been a few case reports of olanzapine causing acute drug-induced reactions. In assessing the safety of olanzapine, it was felt that acute dystonic reactions and akathisia were 'rare' [34]. Landry and Cournoyer in 1998, and Alevizos in 2003, each reported a case of acute dystonia [35,36]. Acute akathisia has been reported more commonly than acute dystonic reactions [37–39]. A large observational Italian study ( $n = 1337$ ) involving patients admitted to a psychiatric intensive care unit and treated with antipsychotics looked at the development of any acute symptoms. A total of 41 patients developed acute dystonic reactions: 32 were treated with typical agents, four with risperidone monotherapy, four with risperidone and later treated with typical antipsychotics, one with quetiapine, and one with olanzapine [40]. Why there have been so few cases of acute reactions compared with other AAs is unclear, but of interest. In a study to determine the effects of larger than usual doses of olanzapine, 30 mg/day and 40 mg/day were used on patients who had been stable on 20 mg/day. Acute akathisia was precipitated in four of 11 (36%) in the 30 mg/day group and in three of 11 in the 40 mg/day group [41].

In a 4-week study of first episode, hence previously untreated patients, no differences were found in the development of parkinsonism or

akathisia between those treated with olanzapine or risperidone [42]. A recent randomized, controlled trial showed that of those psychiatric patients that had either parkinsonism or acute dystonic reactions to typical agents, switching to olanzapine was better than switching to risperidone with respect to management of these movement disorders [22]. However, it is a common experience that olanzapine does cause parkinsonism, and several double-blind, placebo-controlled trials have exposed this problem when the drug was used, at low doses, in treating PD patients with drug-induced psychosis. One study was stopped by the safety monitoring committee [43], and two trials [44], one in Europe and the other in the USA, concluded that the drug should not be used due to motor worsening and its lack of efficacy. We have seen dozens of cases of schizophrenic patients developing parkinsonism on this drug.

Treatment with olanzapine is thought to impart lower risk of developing TD compared with typical antipsychotics both in the short and long term [45–47]; however, there is no published data on patients who have been treated only with olanzapine as their sole neuroleptic. So far as we can determine, there are no cases of TD induced by olanzapine when it was the only antipsychotic drug the patient was exposed to – acute dystonic reactions are very uncommon; however, akathisia and parkinsonism rates are more difficult to determine.

#### ■ Aripiprazole

Aripiprazole is the most recent AA approved by the FDA [203]. It has a novel mechanism that differs from the other atypical neuroleptics in that it is also a partial agonist at D2 receptors. Despite this difference in mechanism, it has also been implicated in a variety of drug-induced movement disorders.

The incidence of akathisia associated with aripiprazole is, like other motor side effects, difficult to untangle. Although a review of the drug published in 2004 [48] reported that the EPS profile was equal to that of placebo, a small study in young nonpsychotic subjects found that eight of 15 with the 'psychosis prodrome' developed acute akathisia on typical doses of the drug [49].

Parkinsonism is readily worsened in patients with PD treated for their psychosis with aripiprazole [50], and has also been seen to induce it in those treated for primary psychiatric conditions [51]. When compared with typical antipsychotics in a Cochrane Database review, it appeared as effective for psychotic symptoms,

with the advantage of fewer occurrences of extrapyramidal manifestations, especially acute akathisia [52]. NMS has been reported in four cases thus far, two of them in the pediatric population [53–55]. Tardive syndromes including TD, dystonia and akathisia have been reported. One case report described how TD, which was induced by another atypical neuroleptic, ziprasidone, was improved with a switch to aripiprazole [56]. Improvement in TDs in other instances have also been mentioned in the literature. Whether these uncommon motor side effects represent some peculiar D2 receptor antagonist properties, or merely some unusual sensitivity of the affected individual, cannot be determined.

Our personal experience has shown that aripiprazole causes parkinsonism in a dose-dependent manner.

### ■ Ziprasidone

Ziprasidone is a benzisothiazole approved by the US FDA in 2001 [203]. It is also a 5HT-1A agonist and inhibits neuronal uptake of serotonin and norepinephrine. It still remains unknown to what degree ziprasidone can induce parkinsonism, with some reports showing that oral or intramuscular administration in PD patients for psychosis management is well tolerated [57,58], and others showing induction of parkinsonism in a schizophrenic patient following intramuscular administration [59]. It should be noted that the latter patient had also been given intramuscular haloperidol for 3 days during the hospital course, and had been on oral olanzapine prior to admission. In the last 3 years, ziprasidone has been associated with acute dystonic reactions in multiple cases [60–63], and an episode of oculogyric crisis in a pediatric patient [64]. The drug is used in parenteral form to quieten agitated patients of all types. Assessing akathisia would be difficult in this setting.

In a large, 4-week study of ziprasidone in schizophrenic and schizoaffective disorders, there was no difference in measures of EPS between ziprasidone and placebo [65].

NMS has been reported in four cases [66–69]. TD has been increasingly reported [70–73], though it seems that only one patient had no known exposure to other neuroleptics. Tardive dystonia has also been described [74–76]. A ‘rebound’ akathisia was described in five women who had never been on other neuroleptics, which developed only on a reduction of the dose of akathisia, but not when the drug was initiated or increased. The duration of exposure was under the time required for the diagnosis of a tardive syndrome [77].

It remains to be seen what the implications of its serotonergic and adrenergic properties are, and it may be too early to draw conclusions from the current available data regarding its profile for inducing or not inducing certain movement disorders.

Our personal experience has shown that ziprasidone may cause parkinsonism at doses typically used to treat psychotic disorders.

### ■ Clozapine

Clozapine was the first of the AAs. It has been shown in a head-to-head trial to be more effective than chlorpromazine [78] and fluphenazine [79], and is thought to be virtually free of most motor side effects [2]. It has been reported to cause neuroleptic malignant syndrome [80]. Only isolated case reports have implicated it as a cause of acute dystonic reactions [81]. In a meta-analysis of 16 studies, Wahlbeck reported that acute extrapyramidal syndromes were significantly less common with clozapine than with first-generation antipsychotics [82].

One study comparing clozapine to chlorpromazine reported that 12% of clozapine-treated subjects developed akathisia, dystonia, rigidity or tremor, versus 25% of chlorpromazine-treated subjects [83]. In the 1988 report leading to clozapine’s release in the USA, clozapine was compared with chlorpromazine plus benzotropine in refractory schizophrenics. Although numbers were not provided, there was significantly less acute EPS with clozapine during the 6-week trial.

The issue of akathisia is much more challenging. One group [84] reported roughly equal incidences of akathisia with chlorpromazine, 5.3%, and clozapine, 6.7%, whereas another study reported 45% with other neuroleptics versus 39% with clozapine [84]. Since clozapine is never used in neuroleptic-naive patients, other than those with idiopathic PD, there is no way to ascertain the true incidence of akathisia. In drug trials there is no mechanism for classifying a withdrawal, or tardive akathisia from an acute syndrome. In addition, there is innate difficulty in distinguishing akathisia from psychotic symptoms themselves, since akathisia, unlike the other EPS, requires a subjective assessment.

The issue of parkinsonism due to clozapine is fairly clear-cut. There are publications involving hundreds of individuals with idiopathic PD or other Parkinson syndromes who have been treated with clozapine, with few reports of motor worsening. In those isolated cases of increased motor disability, it is the opinion of the authors

of this review that this represented either spontaneous worsening of a progressive motor disorder, or was due to the sedation induced by the clozapine. In the two double-blind placebo-controlled trials, each of which involved 60 subjects with advanced idiopathic PD and psychosis, no motor worsening was seen, as assessed by PD experts [85,86]. In fact, there was a trend towards improvement in motor function [85] due to a statistically significant improvement in tremor. In addition, several publications, with no contradictory reports, indicate that tremor is improved by clozapine [87–89], a finding supported by the large double-blind trials.

Clozapine has been reported to both cause and treat Pisa syndrome, an uncommon disorder that may occur acutely or develop after prolonged exposure as a tardive dystonia, but always after exposure to other antipsychotic drugs [90,91].

There are no data on long-term exposure to clozapine in neuroleptic-naïve patients to draw firm conclusions on the development of TD. Tarsy and Baldessarini assert that ‘reports of TD attributable to clozapine have been rare and unconvincing.’ There are reports of TD developing in patients not taking other antipsychotics, but no case had been neuroleptic-naïve [16,92–95]. There are several reports describing the benefits of clozapine on treating TD [96–100], especially tardive dystonia [101–103]. Reports of a tardive syndrome worsening with clozapine withdrawal [104,105] suggests that clozapine may have dopamine receptor blocking motor effects, in that drugs that interfere with dopamine usually suppress or mask choreic syndromes.

### ■ Quetiapine

Indicative of the problems of understanding drug-induced movement disorders in patients switching off medications known to cause these same movement disorders is the report on quetiapine, in which quetiapine was associated with an EPS rate of 6.2%, placebo with a rate of 18% and haloperidol with an EPS rate of 37% [106]. Dystonia occurred in similar low numbers among the three, parkinsonism in 10% of placebo, 5% of quetiapine and 29% of haloperidol, and akathisia in 1% of quetiapine, 8% of placebo and 15% of haloperidol. However, there were no differences in mean EPS ratings for any of the drugs. In addition, there was no dose relationship between quetiapine and EPS. Another study also found no differences between two doses of quetiapine and placebo for EPS. In a prospective open-label study of acute dystonic reactions (ADRs), quetiapine caused an ADR in

15 patients, one of whom had also suffered an ADR on olanzapine, but no ADRs were noted in 152 subjects treated with clozapine [40]. A double-blind, placebo-controlled trial involving 286 schizophrenics found no EPS [107]. A double-blind trial comparing lithium, quetiapine and placebo in 204 entrants found no differences in EPS between quetiapine and placebo; however, the completion rate was low in the placebo group [108].

In a meta-analysis of four double-blind placebo-controlled trials of the effects of quetiapine on mania in bipolar patients [109], the EPS profile for akathisia was identical to that of placebo (13%). The mean change in scores for parkinsonism were also identical in the placebo and quetiapine groups. A small double-blind placebo-controlled trial reported one case of akathisia in nine adolescents who received quetiapine, and none in the placebo group [110].

Quetiapine has been the focus of a large number of open-label studies in PD psychosis, all of which found the drug to be well tolerated in terms of motor function [111]. Two double-blind, placebo-controlled trials found the drug to be nonefficacious for treating the psychosis, but both reported no motor side effects [112]. The American Academy of Neurology has recommended quetiapine as the drug of choice for treating psychosis in PD patients, with clozapine as the second-line drug, due to these compounds being the only antipsychotic drugs that do not cause motor worsening [113].

### Conclusion

Although not properly studied, for the reasons cited in the introduction, it appears that the AA drugs have their individual motor side effects. This is in contrast to the first generation of antipsychotics. The early antipsychotics differed in their likelihood of causing the various drug-induced movement disorders, but every one of them caused every one of the drug-induced movement disorders. Risperidone causes all of the motor side effects associated with the first generation of antipsychotics, but probably at a lower rate, particularly TD [25]. Olanzapine was studied in several double-blind, controlled trials in PD and was found to worsen parkinsonism in each. It clearly causes parkinsonism and akathisia, but rarely causes acute dystonic reactions and has not been associated with TD when it was the only antipsychotic the patient had ever received. Quetiapine has been studied in double-blind, placebo-controlled trials of PD and found not to worsen motor function. It has

been associated with akathisia, rare cases of parkinsonism, but the true incidence of this is difficult to ascertain. There are no reports of acute dystonic reactions or TD when it was the only dopamine receptor-blocking drug the patient had ever received. Ziprasidone has been linked to acute dystonic reactions, akathisia and parkinsonism and, infrequently, to TD. Aripiprazole, although a partial dopamine agonist, was found to worsen parkinsonism in patients with PD. It causes parkinsonism and occasional akathisia, but not acute dystonic reactions or TD in non-PD patients.

The explanation for the differences in motor side effects between the ‘typicals’ and the ‘atypicals’ is debated. The main theories are:

- Selective binding to nonstriatal dopamine receptors, so that psychosis is treated without involving dopamine motor symptoms [17];
- The ratio of serotonin 5-HT<sub>2A</sub> to dopamine D<sub>2</sub> receptor blockade [114], where higher serotonin blockade confers protection from EPS;
- The ‘fast off’ theory, which holds that the freedom from EPS is related to how long the drug binds to the D<sub>2</sub> receptor, which evidently needs to be longer to cause motor side effects than to cause antipsychotic benefits [115].

There is no proof, and therefore no consensus, on the likely explanation.

The important point is that ‘relative’ freedom from EPS is not absolute freedom. Due to the large biological variation and the large number of people treated with the AAs, some people, even without apparent basal ganglia deficiencies, still develop EPS on low doses of these drugs. Some EPS syndromes, parkinsonism in particular, but akathisia also, are dose related, so that some EPS is less likely at low doses. Although there is a general belief that the atypicals have reduced the development of EPS, the tardive syndromes

in particular, the data is limited by the lack of long-term, close follow-up. Some large studies [12] suggest that there may be little or no motor advantage. Recognition of the extrapyramidal syndromes is therefore still an important aspect of good clinical care.

### Future perspective

Psychiatrists will always be interested in treating psychosis with drugs that are more effective, and that have better side-effect profiles than currently available. The development of clozapine proved that antipsychotic effect was not related to motor impairment, a very important theoretical point, since drug screening until then screened purposefully for the development of parkinsonism in animals. This paradigm shift suggested that dopamine D<sub>2</sub> receptor blockade, at least not at the level to cause motor dysfunction, was not a prerequisite for antipsychotic activity.

Currently, pimavanserin, a pure 5-HT<sub>2A</sub> inverse agonist, is being tested as an antipsychotic, and other drugs, with nondopaminergic actions, may follow. The promise of clozapine remains to be realized, but it represents a goal for drug development – an antipsychotic free of movement side effects, yet more effective than the current drugs.

### Financial & competing interests disclosure

*In the past year Dr Friedman has received funds from Astra Zeneca (quetiapine) for talks; consulting and research from Acadia Pharm (pimavanserin) and Neurogen; lectures or research for Novartis (for Parkinson’s disease drugs, but they sell Clozaril®), GlaxoSmithKline, Teva, Boehringer-Ingelheim, Cephalon and EMD Serono. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

*No writing assistance was utilized in the production of this manuscript.*

### Executive summary

- The term ‘atypical antipsychotic’ is loosely used and lacks a consensus definition.
- With the exception of clozapine and quetiapine, all the currently available (USA) atypical antipsychotics may produce extrapyramidal side effects.
- Although it is generally believed that the atypicals are much less likely to produce motor side effects, there is conflicting data on this.
- This review emphasizes the unexplained observation that some atypicals are more likely to cause acute dystonic reactions, others to cause akathisia and still others to cause tardive dyskinesia. Parkinsonism occurs with all but quetiapine and clozapine. This spectrum of different motor disorders with the different atypicals is unlike what had been observed with the first generation of antipsychotics, in which the profiles were quite similar.
- The quest for better antipsychotics with fewer side effects, including motor side effects, must continue.

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