

# Extrapyramidal Effects of First and Second Generation Antipsychotics: A Review

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## ABSTRACT

Antipsychotics are essential for treating major psychiatric disorders like schizophrenia. Second-generation antipsychotics were developed to reduce the risk of extrapyramidal symptoms (EPS) caused by antipsychotic medications. While second-generation drugs have a lower risk of EPS than first-generation treatments, studies show that they can still cause EPS, with clozapine being the least risky and risperidone the most. A literature search of PubMed and Scopus databases until April 2023 found that high doses, a history of past EPS, comorbidities, and specific second-generation medications can increase the risk of EPS. The choice of a first-generation comparator also influences study findings. Although the prevalence and severity of EPS vary with antipsychotics, these medications have not met expectations in terms of tolerability. EPS is still a clinical issue, even in the era of second-generation antipsychotics. This review offers a concise overview of EPS induced by antipsychotics.

**Keywords:** Antipsychotics, Extrapyramidal symptoms, Akathisia, Acute dystonia, Tardive dyskinesia, Drug-induced parkinsonism.

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## INTRODUCTION

Psychosis is a common and disruptive symptom of various psychiatric, neurodevelopmental, neurological, and medical conditions.<sup>1</sup> It is a severe psychiatric condition that is characterized by significant behavioral impairment, an inability to think rationally and comprehend, and a lack of insight. Positive symptoms include hallucinations, delusions, and other abnormal mental experiences, while negative symptoms include impairments in normal functions such as reduced effect, asocial conduct, and low motivation. Poor cognition is indicated by impaired working memory, cognitive speed, and social expectations.<sup>2</sup>

Antipsychotic drugs, also known as “neuroleptics,” are the most commonly prescribed medications for schizophrenia and other serious psychiatric disorders. They are divided into two categories: first-generation antipsychotics (FGAs) or typical psychotics, and second-generation antipsychotics (SGAs) or atypical psychotics.<sup>3</sup> First-generation antipsychotics are dopamine receptor antagonists (DRAs), and examples include chlorpromazine, haloperidol, fluphenazine, trifluoperazine, perphenazine, prochlorperazine, and triflupromazine. Risperidone, olanzapine, quetiapine, ziprasidone, paliperidone, asenapine, lurasidone, iloperidone, clozapine, amisulpride,

and sertindole are FDA-approved second-generation antipsychotics.<sup>4</sup> Some antipsychotics like olanzapine and quetiapine are derived from the clozapine prototype medication.

Since the 1990s, new antipsychotics have been developed to reduce extrapyramidal symptoms (EPS) - the primary side effect of antipsychotics.<sup>5</sup> This review provides a brief overview of recent research on antipsychotics and EPS.

### Extrapyramidal Effects

Antipsychotics work by blocking dopamine receptors, causing extrapyramidal side effects (EPS) such as acute dystonia, akathisia, Parkinsonism, and tardive dyskinesia (TD).<sup>6</sup> EPS can be severe and may require additional treatment.<sup>7</sup> First-generation antipsychotics like haloperidol cause oxidative stress, which contributes significantly to the development of EPS. These side effects, especially drug-induced parkinsonism (DIP) and TD can lead to reduced quality of life and depression in people with schizophrenia.<sup>8,9</sup> The development of EPS occurs in two stages: acute EPS, which occurs early on when starting or increasing antipsychotic medication, and later-onset EPS, which appears as TD after prolonged treatment. The difference between the early EPS and later onset TD is clearly explained in Table 1.<sup>7,10-16</sup>

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**Table 1:** The difference between early EPS and later onset TD, EPS, first generation antipsychotics

<i>Difference</i>	<i>Early- acute EPS</i>	<i>Later-onset EPS (TD)</i>
Frequency	Occurs when antipsychotic medication is first started or when the dose is increased	Occurs after a long duration of treatment
Characterization	Akathisia Acute dystonia Parkinsonism (tremor, skeletal muscle stiffness, and/or bradykinesia)	Involuntary, repetitive facial gestures such as Grimacing Tongue protrusion Oculogyric crises Lips puckering as well as torso and limb motions
Effects on healthcare	Acute EPS are one of the major causes of poor antipsychotic drug adherence	Late-onset TD has the biggest effect on healthcare and careers in terms of quality of life
Nature of symptoms	Acute EPS are reversible	TD can continue for a long time after you stop using your medicine, and it might even be permanent
Prevalence	Acute EPS is thought to develop in around half of individuals treated with high-potency FGAs (such as haloperidol) during the first few days.	The prevalence of TD has been found to range from 0.5 to 70% of patients who get FGAs, with a 24 to 30% frequency

**Acute Dystonia**

Dystonia is characterized by muscular activity that is either intermittent or continuous, with movements ranging from brief jerks to sustained aberrant postures,<sup>17</sup> with supporting references of incidence and prevalence of 25 to 40% of people using atypical antipsychotics. Younger adults and children are more likely to be affected. Dystonia can develop after years of antipsychotic medication, but it can also develop after a much shorter period. It usually affects a single area, but it can affect multiple muscle groups as well. It causes an oculogyric crisis, stiff jaw, tongue protrusion, torticollis, laryngeal and pharyngeal spasm, dysarthria, dysphagia, and occasionally breathing difficulties, cyanosis, and opisthotonus in the cranial, pharyngeal, cervical, and axial muscles.<sup>18</sup> Dystonia is a very unpleasant and sometimes painful condition for patients. About 50% of all cases of acute dystonia are documented in the first two days after starting antipsychotics, and 90% in the first four days.<sup>19</sup> While making a diagnosis, it is critical to rule out neurological illnesses as a cause of antipsychotic-induced dystonia. Anticholinergic drugs like biperiden can effectively prevent or reverse acute dystonia.<sup>18,20,21</sup> Acute dystonic reactions occurred in about 7.2% of those who received long-acting parenteral risperidone.<sup>22</sup> Even case reports of acute dystonia following the start of antipsychotic medication with aripiprazole and ziprasidone have been published.<sup>23,24</sup>

**Akathisia**

Akathisia is a common and significant side effect of antipsychotic medication therapy. Antipsychotics cause one of the most common movement abnormalities, accounting for 50% of EPS.<sup>25</sup> Typically, it occurs within the first three months of treatment. Antiemetics, serotonergic medicines, serotonin reuptake inhibitors, and cocaine can all cause akathisia.<sup>17</sup> Afflicted patients are restless and have a strong desire to move around. They experience distressing feelings of pressure, anxiety, and tension, as well as an increase in motor activity characterized by complex, often purposeless stereotyped, and repetitive movements.<sup>26</sup> The incidence of akathisia among

EPS ranges from 5 to 36.8%. Akathisia occurs in 10 to 20% of patients treated with atypical antipsychotics, compared to 20 to 52% of patients treated with typical antipsychotics.<sup>27</sup> Although akathisia can last throughout antipsychotic medication, it usually resolves once the antipsychotics are discontinued.<sup>28</sup>

Some studies suggest that anticholinergic medications are less effective in the treatment of akathisia, but antipsychotic dose reduction, liposoluble beta-adrenergic blockers, and benzodiazepines have been shown to be helpful.<sup>18,21</sup> A realistic estimate is that akathisia affects about 25% of those on FGAs, but it can also affect those on SGAs. According to some studies, Akathisia rates in FGAs and SGAs are similar.<sup>18</sup> Initially, the SGAs clozapine and quetiapine were thought to have the lowest risk of Akathisia, but this was not confirmed in numerous blinded reviews.<sup>29</sup> Furthermore, The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, which compared the efficacy and side effects of various SGAs to FGA perphenazine in a randomized, partially open-label trial, found that Akathisia is still a problem with SGAs, but at a lower rate than with FGAs.<sup>18,30</sup> For example, a CATIE study showed that risperidone and perphenazine both cause Akathisia in 7% of people. However, the intermediate potency of FGA perphenazine is not universally regarded. Further analysis of the data from the CATIE trial revealed no differences in the incidence of Akathisia and other EPS in chronic schizophrenia patients treated with antipsychotics for up to 18 months in any of the antipsychotics studied.<sup>31</sup> However, when interpreting these findings, the well-known flaws of CATIE (the use of an intermediate-potency FGA perphenazine, and the nonrandomized assignment of tardive dyskinesia patients to SGA treatment) should be considered.

**Parkinsonism**

The most frequent type of Parkinsonism is DIP, which mostly affects older people. DIP symptoms develop shortly after the initiation of antipsychotic therapy<sup>32</sup> and are thought to be caused by the intrinsic antidopaminergic efficacy of the antipsychotic.<sup>33-36</sup> It is best described by the trinity of

bradykinesia, muscle rigidity, and tremor. Resting tremor is less prevalent than postural tremor. The condition known as “rabbit syndrome” is characterized by tremors of the lips and perioral muscles. The frequency is about 15% in people who have used antipsychotics. Parkinsonism is a reversible disorder; DIP symptoms normally improve within a few months after stopping the drug,<sup>37</sup> but in certain individuals, it can reveal neurodegenerative dopamine denervation.<sup>38,39</sup> Parkinsonism has been shown to be strongly linked with the severity of unpleasant symptoms in clinical studies.<sup>40, 41</sup> Parkinsonism caused by antipsychotics is claimed to be chronic in 15% of cases.<sup>42</sup>

For Parkinsonism, dose reduction and anticholinergic drugs may be beneficial. However, anticholinergics should be avoided in geriatrics since they may worsen glaucoma and cause side effects such as cognitive loss, urine retention, dry mouth, and glaucoma aggravation. Although switching to SGAs is commonly recommended in Parkinsonism cases, the rates of Parkinsonism produced by SGAs (e.g., 26% with olanzapine) are lower than those caused by FGAs (55% with haloperidol), but not negligible.<sup>43</sup> According to another study, SGAs have practically no benefit over FGAs in terms of Parkinsonism as a side effect, especially when strength and dose are taken into account. SGAs (such as olanzapine, risperidone, or quetiapine) at high doses induced Parkinsonism at the same rate as low-potency FGAs (chlorpromazine), but the risk was 50% higher in the high-potency FGA group.<sup>44</sup> The findings of the CATIE Parkinsonism study were also mixed. The CATIE study included patients who had previously been excluded from the perphenazine branch due to tardive dyskinesia, which might lead to bias, as patients who had previously been vulnerable to EPS were assigned primarily to the SGA branch. Only participants without a history of TD were included in Parkinsonism comparisons to prevent this possible bias. During the ensuing follow-up period, the proportion of patients with no symptoms of Parkinsonism who satisfied at least one of the three criteria for Parkinsonism did not differ substantially between treatment groups. The covariate-adjusted rates of Parkinsonism were 44% for SGAs and 37% for perphenazine at the 12-month follow-up.<sup>43</sup> Furthermore, the lack of a significant difference in the incidence of Parkinsonism between FGAs and SGAs might be due to the selection of an intermediate-potency FGA (perphenazine) as a comparator in CATIE. The cost utility of the latest antipsychotics in schizophrenia study band 1 (CUtLASS-1) was a randomized controlled trial (RCT) that looked at whether SGAs are superior in terms of clinical and cost-effectiveness in people whose antipsychotic treatment has been changed due to insufficient efficacy or side effects from previous treatment. In this investigation, there was no statistically significant difference in Parkinsonism between SGA and FGA patients across treatment groups.<sup>45</sup> The choice of FGA as a comparator is a major flaw in this study, as it was in the CATIE experiment. Haloperidol was an odd option as a high-potency FGA at first, with sulpiride being the most common. Sulpiride is an unusual FGA with minimal risk of EPS, which has been well-reported.<sup>46</sup>

### Tardive Dyskinesia

Tardive dyskinesia (TD) is a drug-induced movement disorder marked by involuntary, repeated orofacial movements, sometimes accompanied by choreiform upper-extremity movements. It is most commonly associated with antipsychotic medication. The adjective “tardive” indicates a delay after months of antipsychotic medication.<sup>47,48</sup> The movements become more noticeable during the excitement and disappear during sleep.<sup>49</sup>

TD can occur in any patient receiving antipsychotic medication. It typically appears after months or years of continuous antipsychotic use and can last even after antipsychotics are stopped, and it may be irreversible. In long-term studies, the incidence of TD associated with typical antipsychotic therapy is 5% per year in adults and 25 to 30% cumulatively in the elderly.<sup>25</sup> TD does not usually develop within three months. It can, but this is not typical and would be considered the minimal duration of exposure. One to two years is more typical, although it can appear as early as one month in the elderly.

Physicians use an abnormal involuntary movement scale test every three to six months to detect and monitor abnormal movements associated with tardive dyskinesia in patients on antipsychotic medications. It helps clinicians to monitor the effects of these medications as well as researchers studying the effects of these drugs.<sup>50</sup> Anticholinergic medications are not advised because they have been shown to aggravate TD. According to guidelines, the first step is to switch from the causative agent to a second-generation antipsychotic, followed by additional pharmacological treatment if necessary. Margolese *et al.* propose an evidence-based treatment algorithm that includes tapering anticholinergic drugs, switching to a second-generation antipsychotic, and, if necessary, adding tetrabenazine.<sup>51</sup>

Within the first five years of FGA treatment, the chance of developing TD is highest.<sup>21</sup> Due to clozapine’s ability to reduce involuntary symptoms, it has been considered the safest and most effective SGA for TD.<sup>52</sup> A set of prospective cohort studies on TD incidence among outpatients receiving antipsychotic medication on a long-term basis showed SGAs and TD incidence to be poor. While most prior studies suggested that the risk of TD with SGAs is one-quarter that of FGAs, the findings of this study imply that the risk with SGAs is now more than halfway (excluding clozapine patients) or more than two-thirds that of FGAs (including clozapine patients).<sup>50</sup> The study’s unexpectedly high incidence of TD among clozapine patients was blamed on confounding variables such as confounding by indication (prescribing clozapine to patients with TD or at risk for TD), which should be treated with caution. The CATIE study did not include any patients with TD who were given perphenazine. Between antipsychotic medication classes, there were no statistically significant differences in the rate of new-onset TD. The rates ranged from 13% (quetiapine) to 17% (diazepam) (perphenazine).<sup>7</sup> Because patients in the FGA (perphenazine) group had never had TD previously, the CATIE study does not give a true comparison

**Table 2:** Clinical features and risk factors of EPS

<i>Extrapyramidal symptoms</i>		<i>Akathisia</i>		<i>Parkinsonism</i>		<i>Tardive dyskinesia</i>	
<i>Clinical features</i>	<i>Risk factors</i>	<i>Clinical Features</i>	<i>Risk factors</i>	<i>Clinical Features</i>	<i>Risk factors</i>	<i>Clinical Features</i>	<i>Risk factors</i>
<i>Acute dystonia</i>							
Persistent aberrant postures and muscular spasms, especially in the head or neck	Long-term and high-dose antipsychotic use, younger age, male gender, mental retardation, positive family history of dystonia, past dystonic response, and recent cocaine and alcohol use	Restlessness and pacing	Old age, female sex, iron deficiency, negative symptoms, cognitive dysfunction, and affective disorder	Tremor, skeletal muscle stiffness, and/or bradykinesia	Age (elderly), gender (females), cognitive impairment, and early onset EPS	Involuntary, repeated orofacial motions, sometimes accompanied with choreiform upper-extremity movements	Negative schizophrenia symptoms, increased age, non-Caucasian ethnicity, female gender, a history of diabetes, organic brain damage, and a history of diabetes

between FGAs and SGAs in terms of TD, but it does provide some substantial insight into predisposing factors for TD observed at baseline. Some of these factors include advanced age, prior exposure to FGA and anticholinergic drugs, previous longer antipsychotic treatment, and acute EPS.<sup>7,18</sup> TD incidence surprisingly increased in the SGA patient group even during the 12<sup>th</sup> week of therapy in the CUtLASS-1 trial, although this was most likely related to a medication switch (the use of a D2 blocker was stopped, and an SGA with greater anticholinergic effects was started). By the 52<sup>nd</sup> week of the study, the disparity in TD incidence had narrowed.<sup>45</sup>

**DISCUSSION**

Some studies on the ability of FGAs and SGAs to induce EPS has yielded mixed results.<sup>31,43,45,52</sup> Clinical trials may not reflect real-world scenarios in schizophrenia because many patients receive antipsychotic polytherapy in conjunction with other psychotropic drugs (such as antidepressants, anxiolytics, and anticholinergics) with varying degrees of adherence and drug comorbidities, including daily tobacco smoking, which can affect antipsychotic blood levels.<sup>41,53-55</sup> When evaluating this research, methodological issues and limitations such as antipsychotic dosages, the use of an FGA comparator, trial duration, scope and limitations, baseline clinical factors, and the accuracy of the EPS characteristics must all be taken into account. The clinical features and risk factors of EPS were described in Table 2.<sup>10,11,19,28,47,48,56,57</sup>

The collaborative work conducted in the United Kingdom, the United States, and Australia concluded that EPS is robustly predicted by a rebinding model that considers the microenvironment of postsynaptic D2 receptors and integrates association and dissociation rates to calculate the net rate of receptor blockade reversal. As a result, increasing D2 receptor binding kinetics might lead to antipsychotic drugs with a superior clinical profile.<sup>58</sup>

The causative agents, occurrence, and pharmacotherapeutic treatment for EPS were clearly explained in Table 3.<sup>7,17,18,21,22,28,41-43,59</sup>

Though second-generation antipsychotics (SGAs) are indicated as first-line therapy in the treatment of schizophrenia according to current recommendations, they have not quite lived up to their promise of being EPS-free antipsychotics.<sup>60</sup> The efficacy and tolerability of SGAs remain unknown. FGAs, such as haloperidol, cause oxidative stress, which substantially aids in the development of EPS.<sup>61</sup> According to current studies, SGAs are not significantly different from FGAs in terms of efficacy (except clozapine for treatment-resistant patients) and have a lower chance of producing EPS in general than FGAs, despite major variations within the class.<sup>62</sup>

In a study conducted in Italy, EPS was shown to be present in 50.5% of people (144 cases). Tremor was the most common EPS, present in 94 cases (33% of the total sample), often in combination with other forms of EPS. Parkinsonism was the second most prevalent EPS, present in 38 cases (13.3%). Other EPS, such as akathisia (2.1%), TD (1.4%), and acute dystonia (0.7%), were also prevalent.<sup>63</sup> EPS has been associated with reduced treatment adherence,



**Table 3:** Causative medicine, occurrence and therapeutic treatment of antipsychotic-induced EPS

<i>Extrapyramidal symptoms</i>	<i>Causative medicine</i>	<i>Occurrence</i>	<i>Therapeutic treatment</i>
Acute dystonia	FGAs, such as haloperidol, than SGAs, long-acting parenteral risperidone, aripiprazole and ziprasidone, and long-term and high-dose antipsychotics	Occurs after the first four days of treatment	Anticholinergic drugs such as biperiden
Akathisia	Antiemetics, serotonergic medicines, serotonin reuptake inhibitors, and cocaine	Occurs in the first three months of therapy	Liposoluble beta adrenergic blockers, and benzodiazepines
Parkinsonism	First-generation antipsychotics especially chlorpromazine	Emerge anywhere from a few days to many months after commencing treatment	Dosage decrease and anticholinergic medications may be helpful
Tardive dyskinesia	Higher risk in FGAs and some SGAs like quetiapine, diazepam and perphenazine	Occurs after months or years of antipsychotic medication usage	Dosage decrease and switching to SGA and Anticholinergics

worse mental prognosis, and greater mortality in patients with severe mental illness (SMI).<sup>64,65</sup> EPS is more severe and prevalent in individuals with SMI than in those with other mental illnesses, with a higher rate (68–74%) in hospitalized patients.<sup>66,67</sup> Parkinson’s disease (PD) is more likely to occur in patients with bipolar disorder.<sup>68</sup>

Drugs that cause drug-induced parkinsonism (DIP) are more likely to be first-generation antipsychotics (FGAs) than second-generation antipsychotics (SGAs).<sup>69-71</sup> However, selective serotonin reuptake inhibitors (SSRIs), lithium salts, and valproate can also cause EPS.<sup>72-74</sup>

Antipsychotics require antagonism of 60 to 70% of dopamine (D2) receptors to be effective, according to positron emission tomography studies. Blocking 75 to 80% of dopamine (D2) receptors causes acute EPS.<sup>45</sup> Compared to FGAs, the use of SGAs, such as clozapine, is associated with a decreased incidence of movement abnormalities. Goldstein emphasized that long-term clozapine use was not linked to an increased risk of EPS.<sup>75</sup> However, there is little comparable data available for analyzing the risks of atypical antipsychotics inducing EPS.

According to Tarsy, the sequence that causes EPS is clozapine, quetiapine, and olanzapine.<sup>76</sup> Dystonia is an extremely uncomfortable and occasionally painful condition for sufferers. It is one of the most prevalent movement abnormalities produced by antipsychotics, accounting for 50% of extrapyramidal symptoms.<sup>25</sup> In long-term research, the incidence of tardive dyskinesia linked with typical antipsychotic medication is 5% per year in adults and 25 to 30% per year in the elderly. The frequency of TD is dramatically reduced when atypical antipsychotics are used. Patients who have had a brain injury, dementia, mood problems, long-term antipsychotic therapy, anticholinergic and antiparkinsonian drug usage, and a history of EPS are all at risk for TD.<sup>77</sup> A study showed that antipsychotic medications with strong D2 receptor antagonism and illness duration are risk factors for EPS in Chinese patients with schizophrenia.<sup>78</sup> In developing countries like India, EPS is noticed more frequently in those aged 30 to 39 years (34.28%), 40 to 49 years (25.71%), 20 to 29 years (18.57%), and above 50 years (20%). EPS is more common in the 10 to 19 years age group. EPS is moderate in 45% of people, mild in 25.71% of people, and severe in 10% of people. EPS is noticed more commonly in the age group of 10 to 12 years old.<sup>78</sup>

**CONCLUSION**

Extrapyramidal motor problems have a significant impact on patient compliance with antipsychotic drugs, resulting in treatment failure. Therefore, EPS must be adequately recognized and treated to improve drug compliance and efficacy. The possibility of an SGA triggering EPS occurs and depends on some circumstances. The patient’s characteristics (age, gender, and comorbidities), disease history, previous treatment, antipsychotic choice, dose, and duration, as well as adjuvant therapy, should all be considered to decrease the risk of EPS and provide the best possible care. Because treatment results and detrimental effects are not easily foreseeable,

the trial-and-error technique is advised at this time. Perhaps subsequent developments in pharmacogenomics and neurobiology can lead to the creation of antipsychotic response and side effect prediction markers, as well as personalized therapy.

#### AUTHORS CONTRIBUTION

The authors of the manuscript met the criteria for authorship as outlined by the International Committee of Medical Journal Editors (ICMJE). Sharumathi SM played a key role in developing the concepts, acquiring knowledge, and analyzing data. Bhavatharini Sukumaran contributed to the literary quest, while Rinu Mary Xavier drafted the manuscript. Arun K.P assisted with the preparation of the manuscript. The final version of the manuscript was reviewed and revised by Deepalakshmi M.

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