

Review Article

## **Are atypical antipsychotics the least detrimental alternative?**

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### **Abstract**

Antipsychotics are typically used for the treatment of schizophrenia, bipolar disorder, and recently, treatment resistant major depressive disorder. A significant, and very concerning, side effect present with first generation antipsychotics is extrapyramidal symptoms, which are disorders of movement. With the advent of atypical antipsychotics, also known as second-generation antipsychotics, these symptoms are purported to be much less frequent and pronounced than they were with the first generation medications. Numerous hypotheses have been proposed as to why atypical antipsychotics produce fewer extrapyramidal symptoms compared to first generation antipsychotics, which this paper will review. Unfortunately, despite the fact that atypicals have reduced extrapyramidal symptoms in those taking antipsychotics, extrapyramidal symptoms are still an unpleasant and potentially dangerous side effect, which can be difficult to detect, and difficult, or even impossible, to treat. Additionally, atypical antipsychotics result in other potentially very serious side effects, specifically and most commonly, metabolic syndrome, which can decrease life expectancy significantly. However, metabolic syndrome, unlike extrapyramidal symptoms, may be preventable in highly motivated and well-supported patients. Thus, this paper concludes that the benefits of the atypical antipsychotics (reduced extrapyramidal symptoms) outweigh the potential risks for the majority of patients.

**Keywords:** antipsychotics, extrapyramidal symptoms, metabolic syndrome

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## Introduction

Antipsychotic medications are first line recommendation for the treatment of psychotic disorders (i.e. schizophrenia) and bipolar disorder.<sup>1,2</sup> The advent of such antipsychotic medications has had a huge influence on the management of mental illness. The addition of chlorpromazine, the first antipsychotic drug on medical formularies, resulted in a major decrease in the number of institutionalized individuals, thereby improving quality of life for those with serious psychopathology.<sup>3</sup> However, despite numerous benefits, antipsychotics are associated with potentially unpleasant and severe side effects. For example, extrapyramidal symptoms (EPS), which are disorders of movement, may appear hours, months, or even years after the initiation of the medication.<sup>4</sup> Until as recently as the 1980s, it was incorrectly believed that EPS were a necessary aspect of the treatment of psychosis with antipsychotics; in fact, physicians historically used the development of EPS to gauge efficacy of new therapeutic targets.<sup>5</sup>

The introduction of the second generation of antipsychotics (atypical antipsychotics) has generally resulted in a reduction of EPS.<sup>6</sup> However, while it is commonly believed EPS do not occur with the atypical antipsychotics, EPS remain a prominent side effect that must be carefully monitored for over the course of therapy with both first and second generation antipsychotics. This remains the case, despite the fact that atypical antipsychotics differ from first generation (typical) antipsychotics in their mechanisms of action, pharmacokinetics, and pharmacodynamics, as well as in their side effect profile. Within the atypicals as well, there are many pharmacological differences which necessitate categorization.<sup>5</sup> Some argue however that the reduction in EPS is not truly due to such differences, but rather that in the past, the EPS associated with first generation antipsychotics were a result of over-dosing, and not medication type. As such, they propose that the advantage of the atypicals is their relatively lower effective dosing requirements.<sup>5</sup>

Despite the benefit of fewer EPS, due either to different mechanisms or lower dosing requirements, it is also important to consider that atypical antipsychotics have other serious, potentially life threatening side effects, including metabolic syndrome.<sup>7</sup> This paper will review the current literature pertaining to side effects of atypical antipsychotics, including EPS and metabolic syndrome. Specifically, this paper will focus on the proposed hypotheses regarding the mechanisms by which atypical antipsychotics are associated with fewer EPS. This paper will also attempt to determine whether the literature suggests that the atypical antipsychotics are actually superior to the first generation antipsychotics, considering underlying biological, psychological, and social contexts of affected patient populations.

## Atypical antipsychotics

Atypical antipsychotics are a class of medication that are characterized by their supposed reduced risk of EPS at therapeutic doses, a lack of prolactin elevation, and, a significant reduction in positive and negative schizophrenia symptoms.<sup>8</sup> Medications that are classified as

atypical antipsychotics include Clozapine, Risperidone, Olanzapine, Quetiapine, Ziprasidone, Aripiprazole, and Brexpiprazole.<sup>6</sup> These drugs vary greatly in their mechanisms of action, pharmacokinetics, and pharmacodynamics, making it difficult to understand what common factor links them together.<sup>6</sup> Exemplifying the vast differences between the various atypical antipsychotics, Clozapine, the first of this class, has a high affinity for a number of receptors, including, dopaminergic, serotonergic, histaminergic, and muscarinic receptors, with selectivity in the mesolimbic area.<sup>8</sup> Other atypical antipsychotics, such as Risperidone, Olanzapine, Quetiapine, and Ziprasidone mainly act as dopaminergic D2 and serotonergic 5-HT antagonists. Aripiprazole, on the other hand, is a D2 partial agonist.<sup>7</sup> Furthermore, the half-lives of the atypical antipsychotic drugs vary widely; Clozapine has a half-life of 5 to 16 hours, whereas Aripiprazole has a half-life of 75 to 146 hours.<sup>7,8,9</sup> There are even differences in the routes of administration among the atypicals, with some medications being available only in oral formulations (e.g. Clozapine), while others can also be administered intra-muscularly (i.e. Ziprasidone and Aripiprazole). Others including Risperidone and Aripiprazole are also available in long-acting injectable preparations.<sup>7</sup> Finally, the various drugs differ in efficacy for various clinical presentations.<sup>8</sup> For instance, Clozapine is generally effective for treatment resistant schizophrenia, whereas Risperidone is recommended for acute psychosis.<sup>7</sup> Furthermore, some of the atypicals are recommended for the treatment of bipolar mania (e.g. Clozapine, Olanzapine, Ziprasidone), where others are also effective in the treatment of bipolar depression (e.g. Quetiapine). Others have selectivity for the bipolar maintenance phase (e.g. Olanzapine, Aripiprazole, Quetiapine, Risperidone).<sup>7</sup> Furthermore, Risperidone is effective in the treatment of adolescents with psychosis, Aripiprazole is useful as an adjunctive treatment for Major Depressive Disorder, and Quetiapine has been approved as both monotherapy and adjunctive treatment of Major Depressive Disorder.<sup>7,10</sup> Given the wide clinical applications of the various atypical antipsychotics, it is important that we obtain a strong understanding of the potential serious side effects of these medications, including EPS.

## **Extrapyramidal symptoms**

Extrapyramidal symptoms are muscular spasms and other movement difficulties often caused by medications such as antipsychotics. EPS include: parkinsonian motor signs, akathisia (feelings of motor restlessness), dystonia (sustained muscular contraction), and dyskinesia (irregular jerky movements).<sup>4</sup> Some of the characteristics of EPS are similar to those seen in Parkinson's Disease, and thus, it is thought that EPS are associated with a reduction in dopamine signaling, specifically, a D2 blockade in the nigrostriatal region.<sup>11</sup> EPS can be severe and unpleasant, and may interfere with medication adherence.<sup>12</sup> Additionally, these symptoms can be acute (develop within hours or days of taking the medication) or tardive (develop only after chronic exposure to antipsychotics).<sup>4</sup> Due to the different mechanisms of action of the various atypical antipsychotics, these drugs have different risks of producing EPS.

**Table 1.** Comparisons of important parameters of common atypical antipsychotics and binding properties of quetiapine vary depending on the dose.

	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Aripiprazole	Brexpiprazole
<b>Half-life</b>	5-16 hours	20-24 hours	21-54 hours	6-7 hours	6.6 hours	75-146 hours (including active metabolite)	91-177 hours (including active metabolite)
<b>Adminis-tration</b>	Oral	Oral, Depot	Oral acute IM, Depot (not available in Canada)	Oral	Oral, acute IM	Oral, Acute IM, Depot	Oral
<b>Main Mechanism of action</b>	D <sub>2</sub> antagonist, 5HT <sub>2A</sub> antagonist, 5HT <sub>2C</sub> , 5HT <sub>1A</sub> antagonist. Additionally, clozapine has potent antihistamine, anticholinergic, and α <sub>1</sub> -adrenergic antagonism action.	D <sub>2</sub> antagonist, 5HT <sub>2A</sub> antagonist, 5HT <sub>7</sub> antagonist. Additionally, has potent α <sub>1</sub> -adrenergic antagonism.	D <sub>2</sub> antagonist, 5HT <sub>2A</sub> antagonist, 5HT <sub>2C</sub> antagonist. Additionally, has potent antihistamine and anticholinergic action.	D <sub>2</sub> antagonist, 5HT <sub>2A</sub> , 5HT <sub>2C</sub> , 5HT <sub>7</sub> antagonist, 5HT <sub>1A</sub> partial agonist, norepinephrine reuptake blocker. Additionally, has potent antihistamine, anticholinergic, and α <sub>1</sub> -adrenergic antagonism action. <sup>a</sup>	D <sub>2</sub> antagonist, 5HT <sub>2A</sub> antagonist, 5HT <sub>1A</sub> partial agonist, 5HT <sub>2C</sub> , 5HT <sub>7</sub> , 5HT <sub>1B/D</sub> antagonist	Partial D <sub>2</sub> agonist	Partial D <sub>2</sub> agonist
<b>Primary Indications</b>	Treatment resistant schizophrenia, reduction of suicide risk in those with schizophrenia and schizoaffective disorder	Schizophrenia, other psychotic disorders, acute mania, autism related irritability in children, bipolar maintenance	Schizophrenia, acute agitation in schizophrenia and mania, acute mania, bipolar maintenance, bipolar depression, treatment resistant depression	Acute schizophrenia, schizophrenia maintenance, acute mania, bipolar maintenance, bipolar depression, depression	Schizophrenia, acute agitation in schizophrenia, acute mania, bipolar maintenance	Schizophrenia, acute mania, bipolar maintenance, adjunctive treatment in depression, autism-related irritability in children, Tourette's in children, schizophrenia and bipolar related agitation	Schizophrenia, adjunctive treatment for treatment-resistant depression

## Clozapine

In studies, including meta-analyses, comparing Clozapine to first generation antipsychotics, this atypical has been found to produce fewer EPS.<sup>4,13</sup> Research has demonstrated that Clozapine can help significantly reduce tardive dyskinesia in patients already suffering from the disorder, and that it is also less likely to produce this side effect compared to first generation antipsychotics.<sup>7</sup>

However, Clozapine has the rare (0.68%), but potentially life-threatening side effect of agranulocytosis (white blood count  $<1.0 \times 10^3/\text{mm}^3$ ), hence requires strict and regular white blood cell count monitoring which can limit its utility.<sup>14, 15</sup>

## Risperidone

Risperidone has a higher risk of EPS compared to the other atypical antipsychotics. Specifically, EPS with Risperidone appears to be dose dependent, with symptoms tending to emerge at doses higher than 6 mg.<sup>7</sup> Furthermore, although not common, Risperidone is associated with akathisia and dystonia ( $<2\%$ ), even at low doses.<sup>7,16</sup> However, in one randomized double-blind, placebo-controlled study, Risperidone was found to have a significantly lower incidence of EPS compared to Haloperidol (a commonly prescribed first generation antipsychotic) and consequently required less co-prescribed anti-parkinsonian medication to combat these symptoms.<sup>16</sup> Interestingly, the atypicals have been used to reduce severe EPS caused by previous treatment with first generation antipsychotics.<sup>7</sup> Risperidone, in particular, was found to better reduce iatrogenic parkinsonism, akathisia, and tremor when compared to Haloperidol.<sup>17</sup> However, Risperidone also has side effects including metabolic side syndrome and hyperprolactinemia, which can limit the use of this medication.<sup>18</sup>

## Olanzapine

Research has demonstrated that Olanzapine has a lower incidence of EPS compared to the first generation antipsychotics.<sup>5</sup> One paper that examined three randomized, double-blind studies found that Olanzapine resulted in significantly fewer EPS (dystonia, parkinsonism, and akathisia) compared to Haloperidol.<sup>19</sup> Furthermore, a blind, controlled, study found that the appearance of tardive dyskinesia was significantly lower in those taking Olanzapine as compared to typical antipsychotics.<sup>20</sup> However, it is important to note that 2.5%-18% of patients, depending on how EPS is defined, still experienced some form of EPS while on Olanzapine. Although this is significantly lower than the 33.3-46.5% seen with the typical antipsychotic medications, EPS are clearly still a major complication that must be monitored for in those receiving Olanzapine.<sup>18,21</sup>

## Quetiapine

In a double blind, randomized study comparing Quetiapine to Haloperidol, this atypical had significantly lower rates of EPS. Fewer patients required pharmacological treatment for EPS while on Quetiapine, and no participants withdrew due to EPS.<sup>22</sup> Furthermore, studies have found that, on low to high doses (250mg-750mg), EPS rates were comparable to those observed in patients in the placebo (no medication) group.<sup>23</sup>

## **Ziprasidone**

Some patients have found that while on Ziprasidone, they experience either no change, or fewer EPS after four weeks of administration, and rates of EPS are lower when compared to first generation antipsychotics.<sup>24</sup> Furthermore, a double-blind, placebo-controlled study, found that Ziprasidone performed better than placebo in reducing akathisia ratings after one year of drug administration.<sup>25</sup>

## **Aripiprazole**

Aripiprazole is one of the more recently available atypical antipsychotics.<sup>4</sup> In a study comparing Aripiprazole, Haloperidol, and placebo in hospitalized patients, participants experienced fewer EPS on Aripiprazole compared to Haloperidol, with rates similar to those seen in the placebo group.<sup>26</sup> Furthermore, patients were much more likely to discontinue using Haloperidol than Aripiprazole due to EPS (rates of discontinuation being 3% versus 0.8%, respectively). However, it is important to mention that while akathisia ratings were lower in the Aripiprazole group compared to the Haloperidol group, akathisia rates in this atypical were significantly higher than placebo when all doses ranges were considered.<sup>26</sup> This adverse effect can limit its clinical utility.

## **Brexpiprazole**

Brexpiprazole is a relatively new atypical antipsychotic that is marketed as having few adverse effects. Much like Aripiprazole, Brexpiprazole has low levels of EPS at clinical doses. In fact, one study found that incidences of akathisia were lower in the Brexpiprazole group than in the placebo group, and proposed it as a better alternative to Aripiprazole.<sup>27</sup> However, another study found akathisia to be more common in those taking the medication compared to placebo.<sup>27</sup> While there was a higher risk of EPS in those taking 4mg/day compared to 2mg/day, overall the risk of EPS with Brexpiprazole appears to be low.<sup>27,28</sup>

## **Mechanisms of extrapyramidal symptoms reduction**

The various atypical antipsychotics act differently on the brain's neuroreceptors, and there is debate as to why some of these medications have lower incidence of EPS than others, and when compared to the first generation antipsychotics. Some studies have suggested that atypical antipsychotics have a higher antagonistic affinity for the 5-HT<sub>2</sub> serotonin receptors than they do for the D<sub>2</sub> dopamine receptors.<sup>2</sup> Generally, it is believed that EPS are caused by dopamine antagonism in the striatum. Some hypothesize that the serotonin antagonism of the atypicals may help to alleviate EPS by lessening dopamine inhibition in the striatum.<sup>29</sup> Specifically, it is thought that serotonin antagonists act as part of a feedback loop in the basal ganglia, increasing

dopamine release, and that this release eases EPS; however, some evidence exists which challenges this claim.<sup>5</sup> For instance, some of the first generation antipsychotics also have high serotonin antagonism, yet still produce a high degree of EPS.<sup>2</sup> Another more widely supported, hypothesis proposed to describe the mechanism of reduced EPS associated with atypical antipsychotics is that atypicals have a more rapid dissociation from the D2 dopamine receptor as compared to the first generation antipsychotic agents.<sup>30</sup> This is supported by evidence that EPS seems to occur only once D2 occupancy exceeds 80%.<sup>5</sup> Despite preliminary support for the D2 dissociation hypothesis, several questions remain, and further research is required to confirm this mechanism. For instance, if over 80% D2 occupancy is the sole cause of EPS, and a lack of such occupancy the sole cause of EPS reduction, then one would expect no EPS with the atypical antipsychotics, so long as these did not exceed 80% D2 occupancy. However, as previously stated, this is not the case, as EPS still do occur with the atypicals. Furthermore, it does not explain why some EPS occurs years after initiation of the medication.

It is important to have a more complete understanding of the mechanism that underlies the EPS reduction associated with atypical antipsychotics, as this may facilitate the development of targeted treatment to better reduce EPS. In addition, understanding the mechanism behind EPS can help us to better understand potential drug interactions that could exacerbate EPS. Thus, it is essential that more research be conducted towards the elucidation of the mechanisms of EPS and its reduction so that these clinical issues can be addressed.

## **Special considerations for extrapyramidal symptoms**

An important consideration in the administration of atypical antipsychotics is determining which patients are most vulnerable to developing EPS. Despite the fact that this information would be very useful to physicians prescribing such medications, there is relatively little research on the topic. One systematic review that is available on EPS vulnerability found that bipolar patients in a depressive state are at a higher risk of EPS compared to schizophrenic patients, with rates varying depending on the antipsychotic used.<sup>31</sup> Other studies suggest that older patients are at greater risk of parkinsonism effects, perhaps due to an age-related reduction in striatal dopamine, whereas younger patients are at greater risk of developing acute dystonia due to a stronger dopamine response.<sup>5</sup> Recently, one study found that schizophrenic patients who are placed on adjunctive Carbamazepine along with an atypical are also at greater risk for EPS development.<sup>32</sup> This has important implications, since vulnerability to EPS may affect the dose that physicians can safely prescribe before EPS becomes a serious side effect. Preventing these side effects is of particular concern because EPS, and akathisia in particular, results in lower antipsychotic compliance. In fact, there is suggestion that akathisia results in increased suicidality.<sup>12</sup>

There are also several factors which may prevent EPS reduction. First, due to the nature of the disorders that require treatment with antipsychotics, there may be certain cognitive issues that prevent physicians from successfully diagnosing drug induced EPS.<sup>5</sup> For instance, a catatonic patient may be unable to communicate with their healthcare team about their EPS.

Furthermore, it may be difficult for physicians to differentiate between EPS and symptoms of schizophrenia, such as responding to auditory, visual, tactile, and gustatory hallucinations, as well as waxy flexibility.<sup>5</sup> For example, a patient who appears to be muttering to themselves in response to an auditory hallucination, may actually have an oral dyskinesia. Given the unpleasant and potentially serious nature of EPS, it is essential that there exist effective measures of their presence and severity, especially for those patients where diagnosis may be more difficult. Therefore, it is paramount to administer some form of EPS screening. One commonly used approach is the administration of the Abnormal Involuntary Movement Scale (AIMS) at baseline and then regularly after the prescription of atypical antipsychotics to check for the emergence of EPS, especially tardive dyskinesia.<sup>33</sup> This monitoring should allow physicians to make necessary medication adjustments (i.e. changing medications, adding combative medications, or decreasing dosage) to reduce EPS if they occur, and consequently promote patient compliance.

### **Reducing extrapyramidal symptoms**

Given the potentially serious and often unpleasant nature of EPS, it is essential that physicians are educated about methods of reducing these symptoms. Historically, with the first generation antipsychotics, physicians relied on polypharmacy to manage EPS.  $\beta$ -blockers and benzodiazepines continue to remain potential treatment options for those suffering from drug-induced akathisia, although they have limited efficacy.<sup>34</sup> Anticholinergics are another potential option used to offset EPS. Specifically, they can be effective as a short-term prophylactic agents, and have been shown to be particularly effective for the treatment of acute dystonia. However, these medications can cause significant unpleasant side effects, including dry mouth, blurred vision, and confusion.<sup>35</sup> Furthermore, polypharmacy poses several problems in itself. For instance, it increases the risk of other potentially negative side effects, and increases the difficulty in managing these effects. Polypharmacy requires continual monitoring by a physician and careful consideration of the various drug interactions.<sup>36</sup> It is for these reasons that atypical antipsychotics may be a better choice than first generation medications. This is reflected in practice guidelines, which advise lowering dosages, rather than adding medications, as a first response for dealing with atypical antipsychotic-induced EPS.<sup>4</sup>

### **Atypical antipsychotics and metabolic syndrome**

Although atypical antipsychotics are thought to be associated with lower degrees of EPS, other serious side effects that can accompany these medications include Metabolic Syndrome.<sup>37</sup> Metabolic Syndrome is a cluster of conditions, including Obesity, insulin insensitivity, Hypertension, Dyslipidemia (cholesterol and triglyceride abnormalities), and low levels of high density lipoproteins, that often lead to other serious consequences, such as Cardiovascular Disease and Diabetes.<sup>37,38</sup>



Weight gain due to use of atypical antipsychotics is a common and often prohibitive side effect due to its negative effect on patient health and compliance with the medication. This side effect purportedly occurs due to the antagonism of hypothalamic histamine (H1) and serotonin (5HT2c) receptors resulting in increased appetite. Furthermore, although the mechanism is currently unknown, it is thought that second-generation antipsychotics also alter glucose metabolism by increasing insulin resistance.<sup>37</sup> Clozapine, in particular, is associated with a significant amount of weight gain, as well an increased risk of developing Type 2 Diabetes Mellitus.<sup>7</sup> Furthermore, a post hoc analysis of the observational Worldwide Schizophrenia Outpatient Health Outcomes database found that while weight gain is most significant during the first six months of treatment, it persists even years later while continuing to take the medication.<sup>39</sup> Some studies have examined whether these symptoms can be reduced via pharmacological treatments, and indeed, there have been some promising results.<sup>37</sup> For instance, a meta-analysis found that metformin is effective in the reduction of weight gain and insulin resistance.<sup>40</sup> Unfortunately, these positive effects seem to dissipate with cessation of this medication.<sup>41</sup> Recently, studies have also looked at the use of Liraglutide for the treatment of Metabolic Syndrome in those with Schizophrenia taking Clozapine and Olanzapine. It was found that Liraglutide significantly improved glucose tolerance and glycemic control, and also resulted in weight loss.<sup>42</sup> Unfortunately, the need for additional medications in order to combat side effects once again necessitates confrontation of the potential issues associated with polypharmacy. The nature of metabolic syndrome and the treatment it requires puts into question whether the benefits of atypicals (i.e., reduction in EPS liability) outweigh the risks associated with metabolic syndrome. That being said, research has looked into non-pharmacological methods of reducing the risk of metabolic syndrome. Aerobic interval training and strength training has been shown to have promising results towards this end.<sup>43</sup> Other studies have shown that placing patients on weight-management programs significantly helps with weight loss, and prevention of further weight gain in patients on atypical antipsychotics. Notably, the effectiveness of various therapeutic interventions depends on the characteristics of the patient. For instance, those with chronic Schizophrenia respond better to recreation-type interventions, with the added benefit that these also aid in future social interaction. On the other hand, younger individuals with recent-onset psychosis tend to respond more favourably to more flexible, individualized therapies that involve diet, exercise, and behavioural modifications.<sup>44</sup>

Unfortunately, many of the studies looking at Metabolic Syndrome in those taking atypical antipsychotics focus on weight loss after Metabolic Syndrome has already taken effect. There are considerable gaps in the literature regarding effective preventative methods. However, one study found that weight gain was significantly reduced in patients that underwent a nutrition management program (promoting diet, exercise, and healthy food intake) in those starting Olanzapine.<sup>45</sup> Given these promising results, it seems that Metabolic Syndrome can be prevented in some patients through non-pharmacological therapeutic interventions. However, it is clear that further research needs to be conducted on the prevention of Metabolic Syndrome on those taking atypicals. Specifically, different non-pharmacological treatments should be considered, and the

effectiveness of various treatments should be tested with for each atypical and with different populations (e.g., chronic vs. recent-onset psychosis, young vs. older patients, patients of different ethnicities, etc.). Once this information is available, physicians will be better able to understand the metabolic consequences of prescribing atypical antipsychotics, and will be better equipped to help patients avoid the serious risks associated with metabolic syndrome. If future studies suggest that Metabolic Syndrome can be effectively prevented via non-pharmacological therapies, then the risk-benefit ratio would likely favour the atypical antipsychotics as compared to the first generation antipsychotics. This would go a long way toward increasing physician comfort and confidence in prescribing atypicals to their patients.

## **Future directions**

Overall, it appears that the atypical antipsychotics are a superior treatment for psychosis as compared to the first generation antipsychotics. This is especially true with regard to the recent atypicals that are emerging on the market, some of which are favourable with respect not only to EPS, but also with respect weight gain and metabolic effects. The atypicals as a class, have lower EPS liability, and studies support that Metabolic Syndrome associated with treatment with atypical antipsychotics can be at least somewhat controlled with interventions involving diet and exercise.<sup>44</sup> That being said, more research needs to be conducted on the various atypical antipsychotics and how they affect patient quality of life. Specifically, it is important that we develop a greater understanding of the impact in this regard of both EPS and metabolic syndrome on these patients. Future research should delve into the demographics (e.g., age, sex, ethnicity, type of disorder, occupation, etc.) of individuals being treated with antipsychotics, and attempt to determine the risk-benefit profile for each group. Although it is important to carefully monitor for both of these side effects, and ideally, we would prefer that patients experience neither, it is possible that a specific patient population may be more susceptible to developing one side effect over another. In other words, certain groups might report a lower negative impact upon quality of life with EPS. For example, someone who is already significantly overweight with a positive family history of diabetes may be less impacted by the metabolic side effects of atypical antipsychotics than someone whose livelihood involves excellent fine motor control may be effected by EPS. This information is important, as it could help to inform value-sensitive prescribing. Specifically, it would assist clinicians in determining which antipsychotic should be prescribed to each individual patient based on the least detrimental side effect profile for that individual.

Another important consideration in the prescription of atypical antipsychotics is drug interactions. Although extensive research has been conducted on how various drugs react with the atypical antipsychotics, specifically with regard to research involving enzyme metabolism, relatively little work has been done to investigate how drug interactions affect EPS.<sup>46</sup> Further research should be conducted in this area to help prevent EPS in patients taking atypical

antipsychotics together with other medications, including for augmentation, as well as for comorbid psychiatric and medical conditions.

## Conclusion

The current available literature suggests that the atypical antipsychotics appear to be a better alternative than the first generation antipsychotics. While this really is a matter of finding the treatment with the least detrimental side effects (i.e. EPS vs. Metabolic Syndrome) on a case-by-case basis, overall the atypicals have lower EPS risk. Furthermore, Metabolic Syndrome, while certainly serious, can be more effectively treated, and perhaps even prevented, with non-pharmacological interventions. The research suggests that pharmacological agents, while not ideal in either case, seem to be more effective in combating Metabolic Syndrome than EPS. However, it is still vitally important that physicians are aware of the risks associated with the atypical antipsychotics, including EPS, and that patients on these medications are extensively and regularly monitored for the associated side effects. Finally, it is clear that more research needs to be conducted on the atypical antipsychotics and the significant side effects associated with them. Particular attention should be paid to understanding the mechanisms of both EPS and Metabolic Syndrome, and the impact these side effects have upon patients' quality of life.

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