

# Specific mechanism of action of amisulpride in the treatment of schizophrenia and correlation with clinical response and tolerability

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**Abstract:** The treatment of schizophrenia has advanced because the therapeutic efficacy, tolerability, and safety profiles of atypical antipsychotics seem to be superior to those of classical neuroleptics. Amisulpride is an atypical antipsychotic drug with a unique receptor pharmacology, which is dose-dependent. As could be predicted from the pharmacologic profile of a pure D2/D3 receptor blocker, amisulpride is an atypical antipsychotic agent, effective for positive and negative symptoms, which can bring about additional improvement in the social functioning and quality of life of patients with schizophrenia. Amisulpride has one of the lowest potentials for weight gain of all the antipsychotic agents, and is clearly associated with lower use of anti-parkinsonian medication and with fewer dropouts due to adverse events than conventional antipsychotics. Amisulpride is well tolerated in terms of anxiety and insomnia. Amisulpride has a pronounced prolactin-elevating effect which appears to be independent of dosage and duration of administration. Hyperprolactinemia rapidly reverses after amisulpride discontinuation. Amisulpride benefits patients with negative symptoms, and is the only antipsychotic to demonstrate efficacy in patients with predominantly negative symptoms. Amisulpride maintains its efficacy when used for medium-/long-term treatment, as demonstrated in studies of up to 12 months. Amisulpride has the best evidence as an effective adjunct to clozapine treatment. In conclusion, amisulpride is an antipsychotic agent with proven efficacy and good tolerability.

**Keywords:** antipsychotic agents, amisulpride, adverse events, pharmacology

## Introduction

Forty years ago few neuroleptics were available to psychiatrists. These were all compounds today known as conventional antipsychotics, and all were liable to cause severe extra-pyramidal side-effects (EPS). Nowadays, new treatments are more ambitious, aiming not only to improve psychotic symptoms, but also quality of life and social reintegration. However, adverse effects, such as movement disorders and sedation, are problematic and can result in noncompliance with medication. Positive symptoms, such as delusions, hallucinations, and thought disorders, are more often experienced in the acute phases of the illness than are negative symptoms, such as poverty of speech, lack of motivation, apathy, and inability to express emotions.<sup>1</sup>

## Atypical antipsychotics

“Atypical” is a term widely used to describe some antipsychotics with specific characteristics, such as minimal risk of acute and chronic movement disorders and less sedation.<sup>2</sup> The atypical antipsychotic drugs are also thought to be more effective than conventional drugs in the treatment of negative symptoms in schizophrenia, although

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this has not yet been adequately established.<sup>3</sup> At present, new antipsychotics are routinely investigated for their possible effect on negative symptoms.

The term atypical has been used too loosely for it to have a robust scientific meaning. Yet the marked frequency of its use, coupled with the failure of more scientifically reliable terms to replace it, suggests that the term conveys a valuable meaning.<sup>4</sup> It was first introduced to describe clozapine, since its properties were found to be different from the older, conventional, or typical neuroleptics.<sup>5</sup> The term atypical was then accepted as including the characteristics common to those antipsychotic drugs developed more recently, including: (a) absence of hyperprolactinemia; (b) greater efficacy in treating positive and negative symptoms and symptoms of disorganization; and (c) absence of tardive dyskinesia or dystonia after being administered chronically.<sup>6–8</sup>

The atypical drugs differ from the typicals in their mechanism of action, but not all share the same mechanism. Clozapine, the prototype of these agents, has been found to improve delusions and hallucinations in patients who fail to respond to other antipsychotic drugs, and to reduce the risk of suicide. These agents have been found to increase cortical dopamine and acetylcholine release, as well as to have a variety of effects on the glutamatergic system not shared by the typical agents.<sup>7</sup> At least in clinical circles, most would agree that clozapine, risperidone, olanzapine, quetiapine, sertindole, ziprasidone, aripiprazole, and amisulpride are atypical, even though many of those agreeing to the above list may disagree on the criteria of definition. Atypical antipsychotics show fewer EPS than older antipsychotic drugs and require less concomitant anticholinergic use, even when controlling for the high doses of haloperidol that have been conventionally used in such studies.<sup>9,10</sup>

The second most commonly shared feature is that most of the newer atypical antipsychotics show either no, or only transient, prolactin elevation. The two notable exceptions in this regard are risperidone and amisulpride, and it is now understood that this exception may largely be attributed to these drugs having a higher peripheral/central distribution ratio, thereby leading to excessive dopamine blockade in the pituitary that lies outside the blood–brain barrier.<sup>11</sup>

## Amisulpride

Amisulpride is a highly selective dopamine D2-like receptor antagonist ( $K_i = 2.8$  nmol/L for D2 receptors and  $K_i = 3.2$  nmol/L for D3 receptors), with several orders of magnitude higher affinity for D2/D3 receptors than any other receptor population.<sup>12</sup> A positron emission tomography study

of amisulpride-treated patients found no significant binding to 5-HT<sub>2A</sub> receptors.<sup>12</sup> In clinical trials, amisulpride has shown therapeutic benefit, with a profile of side-effects similar to that of placebo.<sup>13</sup> This and its highly specific receptor profile make it ideally suited to test whether antipsychotic efficacy and a low incidence of EPS may be achieved purely by selective action at limbic cortical dopamine D2/D3 receptors *in vivo*.<sup>14,15</sup>

## Specific mechanism of action of amisulpride

Most new antipsychotics introduced onto the market in the past two decades (eg, risperidone and olanzapine) have been multireceptor-acting agents, especially having concomitant 5-HT<sub>2</sub> receptor antagonism.<sup>16</sup> A notable exception to this has been amisulpride, a benzamide derivative that has high and similar affinities for the dopamine D2 and D3 receptor subtypes and is devoid of any significant affinity to other receptor systems.<sup>12</sup> Yet, amisulpride shows most of the attributes of atypicals, ie, a lower risk of EPS, a somewhat greater improvement in positive and negative symptoms, and better overall outcome in longer-term follow-up studies compared with more conventional serotonin-dopamine or multireceptor atypical antipsychotics.<sup>13,14</sup>

Amisulpride is a unique atypical antipsychotic that selectively blocks D2 and D3 receptors presynaptically in the frontal cortex, possibly enhancing dopaminergic transmission, and postsynaptically in the limbic areas, possibly reducing it. Thus, dopaminergic overactivity in the frontal cortex and underactivity in the limbic areas, can be treated simultaneously, alleviating both positive and negative symptoms of schizophrenia, respectively.<sup>17</sup> Additionally, the finding that amisulpride is a highly effective antidepressant via antagonism at 5-HT<sub>7</sub> receptors would make its mechanism of action unique relative to other approved antidepressant drugs, and supports the development and/or testing of more selective 5-HT<sub>7</sub> receptor antagonists to treat depression in humans.<sup>18</sup>

## Amisulpride in schizophrenia

Amisulpride is an atypical antipsychotic with a significantly greater effect size than first-generation, typical antipsychotics, and efficacy at least similar to that of olanzapine and risperidone in large-scale clinical trials in schizophrenia. Amisulpride provides greater improvement in positive and negative symptoms of schizophrenia, a better long-term outcome than typical antipsychotics, and distinct tolerability advantages over typical antipsychotics, which are

reported to cause EPS in 20% to 50% of patients.<sup>16–18</sup> There is little evidence from randomized controlled trials comparing amisulpride with other second-generation antipsychotic drugs. We could only find trials comparing amisulpride with olanzapine, risperidone, and ziprasidone. Amisulpride may be particularly suitable for clozapine-augmentation therapy in patients with refractory schizophrenia. Indeed, amisulpride is more effective than quetiapine as augmentation therapy in patients partially responsive to clozapine, and several prospective open-label studies and case series have reported promising results for amisulpride/clozapine combination therapy.<sup>13,17,19</sup> The pharmacological and clinical profiles of amisulpride suggest that this agent is a viable clinical option when a change of antipsychotic therapy is required in patients with schizophrenia because of lack of efficacy, adverse events, and poor adherence to treatment, or for augmentation of clozapine in treatment-resistant illness.<sup>13</sup> Amisulpride has a pronounced prolactin-elevating effect which appears to be independent of dosage and duration of administration. Hyperprolactinemia rapidly reverses following amisulpride discontinuation.<sup>19</sup> Amisulpride overdose commonly causes QT prolongation, bradycardia, and hypotension. Torsades de pointes occurred commonly enough to suggest that amisulpride is highly cardiotoxic in overdose.<sup>1,13,19</sup>

## Clinical response

Leucht et al<sup>19</sup> have recently conducted a meta-analysis comparing nine second-generation antipsychotics with first-generation drugs for overall efficacy, positive, negative, and depressive symptoms, relapse, quality of life, EPS, sedation, and weight gain. Results showed that five second-generation drugs (aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine) were not significantly different from first-generation antipsychotics in their effects on overall, positive, and negative symptoms, whereas clozapine, amisulpride, olanzapine, and risperidone were more efficacious than first-generation drugs. Olanzapine, risperidone, and sertindole proved to be significantly better than first-generation drugs on relapse prevention. For quality of life, only clozapine, sertindole, and amisulpride were better than first-generation drugs.<sup>19</sup>

Choosing the right antipsychotic is one of the most challenging issues when treating schizophrenia. Next to efficacy issues, safety of medication, including subjectively distressing side-effects (sedation, hypersalivation or dry mouth, akathisia, sexual dysfunction) with negative medical consequences (weight gain, orthostatic hypotension, diabetes, hyperprolactinemia, corrected QT prolongation) and life-threatening adverse events (agranulocytosis, neuroleptic malignant

syndrome), also influence the choice of medication.<sup>20,21</sup> Some meta-analyses have identified clozapine, amisulpride, risperidone, and olanzapine as being significantly more effective than first-generation (typical) antipsychotics and other second-generation (atypical) antipsychotics<sup>14,19</sup> (see Table 1). However, there is little evidence from randomized controlled trials comparing amisulpride with other second-generation antipsychotic drugs. There are just a few trials comparing amisulpride with olanzapine, risperidone, and ziprasidone. We found that amisulpride may be somewhat more effective than ziprasidone, and more tolerable in terms of weight gain and other associated problems than olanzapine and risperidone. These data, however, are based on only 10 short- to medium-term studies and therefore too limited to enable firm conclusions.<sup>22</sup>

Clinically, amisulpride is characterized by a side-effect profile most resembling that of an atypical antipsychotic due to its low EPS burden.<sup>13</sup> However, like risperidone and first-generation antipsychotic drugs, amisulpride causes large elevations in serum prolactin levels, most likely due to its potent D2/D3 antagonist properties.<sup>23</sup> Thus, despite having a pharmacologic profile reminiscent of a typical antipsychotic in that it exhibits high D2 affinity and low 5-HT<sub>2A</sub> affinity, amisulpride therapeutically resembles atypical antipsychotics. The identification of the 5-HT<sub>7a</sub> receptor as a target blocked by amisulpride suggests a plausible explanation for its antidepressant efficacy. Changes in 5-HT<sub>7</sub> receptor function have been shown to result from chronic antidepressant treatment.<sup>14–16</sup> The 5-HT<sub>7a</sub> receptor antagonism, and not D2/D3 receptor antagonism, likely underlies the antidepressant actions of amisulpride.<sup>16</sup> Moreover, 5-HT<sub>7</sub> receptor antagonists and presently approved antidepressants also appear to have similar effects on hippocampal neurogenesis.<sup>16,17,24</sup> Kapur and Seeman propose that fast dissociation from the D2 receptor makes an antipsychotic more accommodating of physiological dopamine transmission, allowing an antipsychotic effect deprived of motor side-effects, prolactin elevation, or secondary negative symptoms.<sup>25</sup>

## Tolerability

Amisulpride has an improved safety and tolerability profile, and has been shown to be significantly more effective than placebo and haloperidol on a number of quality of life and social functioning scales, including the Global Assessment of Functioning, the Quality of Life Scale, the Functional Status Questionnaire, and the Psychosocial Aptitude Rating Scale.<sup>26</sup>

**Table I** Inhibitory effects of amisulpride against radio ligand binding in vitro

	Receptor		Radioligand	IC <sub>50</sub> (mM) Amisulpride
Dopamine	D <sub>1</sub>		[ <sup>3</sup> H]SCH23390	>10
	D <sub>2</sub>		[ <sup>3</sup> H]spiperone	0.021
	D <sub>3</sub>		[ <sup>3</sup> H]7-OH-DPAT	0.0029
	Transporter		[ <sup>3</sup> H]GBR12935	>100
Noradrenaline	α <sub>1A</sub>		[ <sup>3</sup> H]prazosin	7.1
	α <sub>1B</sub>		[ <sup>3</sup> H]prazosin	14.1
	α <sub>2</sub>		[ <sup>3</sup> H]clonidine	1.6
	β		[ <sup>3</sup> H]dihydroalprenolol	>10
	Transporter		[ <sup>3</sup> H]desipramine	>10
5-HT	5-HT <sub>1A</sub>		[ <sup>3</sup> H]8-OH-DPAT	>10
	5-HT <sub>1B</sub>		[ <sup>3</sup> H]5-HT	>10
	5-HT <sub>1D</sub>		[ <sup>3</sup> H]5-HT	>10
	5-HT <sub>2A</sub>		[ <sup>3</sup> H]spiperone	2.0
	5-HT <sub>2C</sub>		[ <sup>3</sup> H]mesulergine	>10
	5-HT <sub>3</sub>		[ <sup>3</sup> H]quipazine	>10
	5-HT <sub>4</sub>		[ <sup>3</sup> H]GR113808	>10
ACH	M		[ <sup>3</sup> H]QNB	>100
Histamine	H <sub>1</sub>		[ <sup>3</sup> H]pyrilamine	>10
GABA	A	GABA	[ <sup>3</sup> H]GABA	>100
		ω <sub>1</sub>	[ <sup>3</sup> H]flumazenil	>100
		ω <sub>2</sub>	[ <sup>3</sup> H]flumazenil	>100
		ω <sub>3</sub>	[ <sup>3</sup> H]flumazenil	>10
		Channel	[ <sup>3</sup> H]TBOB	>100
	B		[ <sup>3</sup> H]GABA	>100
	Transporter		[ <sup>3</sup> H]nipocotic acid	>100
Glycine (strychnine-sensitive)			[ <sup>3</sup> H]strychnine	>10
Glutamate	NMDA	Glutamate	[ <sup>3</sup> H]CGP39653	>100
		Glycine	[ <sup>3</sup> H]Glycine	>100
		Polyamine	[ <sup>3</sup> H]ifenprodil	>10
		Channel	[ <sup>3</sup> H]MK801	>10
	AMPA		[ <sup>3</sup> H]AMPA	>100
	Kainate		[ <sup>3</sup> H]Kainate	>100
Adenosine	A <sub>1</sub>		[ <sup>3</sup> H]PEA	>10
	A <sub>2</sub>		[ <sup>3</sup> H]NECA	>10
Angiotensin II	AT <sub>1</sub>		[ <sup>3</sup> H]angiotensin II	>10
	AT <sub>2</sub>		[ <sup>3</sup> H]angiotensin II	>10
Ca <sup>++</sup> channel	L		[ <sup>3</sup> H]nitrendipine	>10
Na <sup>+</sup> channel			[ <sup>3</sup> H]batrachotoxinin A	>10
P-site (BZP)			[ <sup>3</sup> H]RO5-4864	>10
Imidazoline	I <sub>2</sub>		[ <sup>3</sup> H]idazoxan	>10
Sigma			[ <sup>3</sup> H]ifenprodil	>10

In spite of their better tolerability profile, CATIE (the Clinical Antipsychotic Trials of Intervention Effectiveness) showed a high dropout rate with atypical antipsychotics because of either inefficacy or intolerable side-effects.<sup>27</sup> The atypical antipsychotic drugs are a class of agents that have become the most widely used to treat a variety of psychoses because of their superiority in terms of EPS. The major concern about the safety of the atypical antipsychotics is related to their propensity to induce weight gain and alter glucose

and lipid metabolism. Their main clinical advantage beyond low EPS is their ability to improve cognition (to some extent), which is one of the key deficits in schizophrenia. Several studies have found that amisulpride and risperidone are better tolerated than haloperidol in terms of EPS.<sup>28–30</sup>

Metabolic side-effects have been found earlier during treatment with second-generation antipsychotics. Weight gain might contribute to their risk of morbidity and mortality by leading to an increase in lipid dysregulation, hypertension,

Table 2 Atypical antipsychotics vs conventional low-potency antipsychotics

	At least one EPS			No clinically significant response			Anti-parkinsonian medication			Dropouts because of adverse events		
	N	n	RD (95% CI)	P	N	n	RD (95% CI)	P	N	n	RD (95% CI)	P
Amisulpride	1	30	0 (-0.29 to 0.29)	1.0	1	30	0.07 (-0.24 to 0.37)	0.7	1	30	0.00 (-0.18 to 0.18)	1.0
Clozapine	11	758	-0.15 (-0.26 to -0.04)	0.008	7	685	-0.15 (-0.27 to -0.03)	0.02	3	125	-0.01 (-0.05 to 0.03)	0.7
Olanzapine	4	194	-0.15 (-0.31 to 0.01)	0.07	4	194	-0.22 (-0.42 to -0.02)	0.03	NI	ND	-0.03 (-0.10 to 0.04)	0.4
Quetiapine	1	201	0.03 (-0.07 to 0.13)	0.6	1	201	-0.13 (-0.27 to 0.00)	0.05	1	201	-0.05 (-0.12 to 0.02)	0.14
Risperidone	1	42	-0.10 (-0.30 to 0.11)	0.4	1	42	-0.29 (-0.56 to -0.01)	0.04	1	42	-0.10 (-0.24 to 0.05)	0.2

Data from De Oliveira and Jurueña;<sup>46</sup> American Psychiatric Association 2008;<sup>46</sup> Jurueña et al.<sup>50</sup>**Abbreviations:** EPS, extra-pyramidal side-effects; N, number of trials included in the analysis; n, total number of patients included in the analysis; RD, risk difference for comparison with low-potency conventional antipsychotics; NI, not indicated; ND, no data.

type 2 diabetes mellitus, cardiovascular disease, and other related diseases.<sup>31,32</sup> In addition, being overweight usually leads to lower self-image and self-esteem, decreased quality of life, and social disadvantages, and is associated with medication noncompliance.<sup>33–35</sup> Recently, metabolic syndrome in patients with schizophrenia has drawn enormous attention from researchers. Previous studies showed that approximately 7% to 60% of patients with schizophrenia-related disorders have metabolic syndrome.<sup>36,37</sup> Most studies show that the prevalence of metabolic syndrome in patients with schizophrenia or schizophrenia-related disorders is higher than that in the normal population.<sup>37,38</sup> Weight gain was also shown to be significantly greater with risperidone than with amisulpride (1.4 kg vs 0.4 kg,  $P = 0.026$ ).<sup>39</sup>

In a 6-month treatment period, significantly fewer amisulpride-treated patients presented a weight increase of 7% or higher than that of baseline compared with those receiving risperidone (18% vs 34%).<sup>40</sup> Additional evidence for decreased levels of weight gain in amisulpride-treated patients relative to olanzapine-treated patients comes from both an 8-week study (weight gain in the olanzapine vs the amisulpride group 2.7 + 3.9 kg vs 0.9 + 3.2 kg, respectively) and a 6-month study (weight gain in the olanzapine vs the amisulpride group 3.9 kg + 5.3 vs 1.6 + 4.9 kg, respectively).<sup>41,42</sup>

Recently, a meta-analysis of all randomized and double-blind studies demonstrated that amisulpride treatment was significantly associated with relatively low weight gain.<sup>43</sup> Collectively, these findings suggest that amisulpride is an atypical antipsychotic drug with a lower risk of weight gain. Both amisulpride and ziprasidone were preferred to olanzapine in patients who had recently experienced weight gain.<sup>44,45</sup> This makes sense because second-generation antipsychotics do not appear to differ in efficacy, but both amisulpride and ziprasidone have been shown to cause less weight gain than other compounds.<sup>42,46,47</sup>

During the treatment course, the amisulpride-treated patients showed significantly decreased fasting triglyceride, total cholesterol, glucose, and insulin resistance levels, decreased diastolic blood pressure and pulse rate, and a significant increase in high-density lipoprotein cholesterol levels after switching to amisulpride (all  $P < 0.05$ ). The prevalence of metabolic syndrome in amisulpride-treated patients also decreased significantly from 65.2% to 30.4% ( $P < 0.001$ ). These findings suggest that switching to amisulpride could be an effective treatment of overweight or obese psychiatric patients treated previously with other second-generation antipsychotics.<sup>48</sup>



Rettenbacher et al<sup>49</sup> conducted a prospective, open study in schizophrenia patients in order to compare body weight and serum lipids during treatment with amisulpride, ziprasidone, clozapine, or olanzapine over a period of 4 weeks. In patients treated with amisulpride or ziprasidone, the authors found a decrease in body mass index and total cholesterol whereas high-density lipoprotein cholesterol increased. These results indicate that treatment with ziprasidone and amisulpride is more favorable than treatment with clozapine and olanzapine for the risk of inducing weight gain and hyperlipidemia. These results are important for the increased risk for cardiovascular complications in patients with schizophrenia. In addition to weight reduction, this study showed that the lipid profiles in these overweight or obese patients also improved significantly. A growing body of evidence indicates that use of some atypical antipsychotics, including clozapine and olanzapine, may be linked to impairment in some health-related lipid indices.<sup>50</sup>

## Conclusion

In conclusion, amisulpride, in addition to its proven clinical efficacy, may help social reintegration of the schizophrenic patient. The negative symptoms of schizophrenia are characterized by poverty of speech, blunted affect, lack of initiative, poor motivation, and a general slowness and underactivity, all of which result in social withdrawal. This may reflect the fact that new-generation antipsychotics have more distinct differences in their safety and tolerability profiles than in their efficacy characteristics.

Although this knowledge helps to guide clinicians in drug choice, the translation of clinical trial findings into individual patient needs remains a daunting challenge. Cognitive impairment also plays a role in occupational and social functioning.

Recent data indicate that, for the atypical antipsychotic amisulpride, these properties can be translated into a better quality of life, and enhanced social functioning and reintegration into society.

## Disclosure

The authors report no conflicts of interest in this work.

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