

# Atypical antipsychotics in Schizophrenia - a short guide





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# Introduction

Before the advent of the atypical, or second-generation, antipsychotic agents, patients with schizophrenia were typically prescribed conventional or 'typical' antipsychotics with the associated limitations of poor efficacy against negative symptoms and unwanted extrapyramidal symptoms (EPS), particularly at higher doses.<sup>1-3</sup>

Due to the different receptor-binding properties of the atypical antipsychotics, these agents confer a lower risk of EPS compared with conventional agents and some beneficial effects on the negative and cognitive symptoms of schizophrenia.<sup>1,3</sup>

However, the atypical agents are not without their problems. Antagonism of dopamine D<sub>2</sub> receptors underlies the efficacy of all of these agents against psychotic symptoms, thus EPS still remain an issue with high-dose treatment. Although there are differences between the atypical agents, they also confer risks of sedation, metabolic disorders, and sexual dysfunction.<sup>1,2</sup>

In order to achieve successful treatment and long-term compliance, it is crucial to assess the risks and benefits of available treatments and individual patient needs. This booklet will evaluate the mechanisms of action and factors influencing the risk-benefit profiles of the available atypical antipsychotics in order to illustrate how these agents compare.

For issues related to Cardiac tolerability and safety see: "To the heart of ECG: a pocket guide for psychiatrists".

# Mode of action of the atypical antipsychotics

## Dopamine D<sub>2</sub> blockade with typical antipsychotics

- Typical antipsychotics bind with high affinity to D<sub>2</sub>-like dopamine receptors (Table 1)<sup>4,5</sup>
- Dopamine D<sub>2</sub> blockade in the subcortical limbic areas (e.g. nucleus accumbens) reduces positive symptoms of schizophrenia
- Studies have shown that striatal dopamine D<sub>2</sub> receptor occupancy of 65–70% is sufficient to produce an antipsychotic effect with the D<sub>2</sub> antagonist antipsychotics<sup>1,5</sup>
- A dopamine D<sub>2</sub> receptor occupancy of >80%, which is normally needed to obtain an antipsychotic effect with conventional agents, usually induces EPS<sup>5</sup>
- Blockade of muscarinic, adrenergic and histaminergic receptors by typical antipsychotics is also associated with worsening of cognitive symptoms and other side effects:<sup>1</sup>
  - Muscarinic receptor blockade: dry mouth, dimmed sight, constipation, urinary retention, cognitive disturbance
  - Adrenergic  $\alpha_1$  receptor blockade: orthostatic hypotension, sedation
  - Histaminic H<sub>1</sub> receptor blockade: weight gain, sedation

## Dopamine D<sub>2</sub> blockade with atypical antipsychotics

- Some atypicals exhibit lower affinities for the dopamine D<sub>2</sub> receptor than conventional agents. Lower affinity may contribute to the fewer extrapyramidal side effects associated with these atypicals compared with typical agents<sup>4,6,7</sup>
- However, it is more likely that relative affinities of atypicals for a number of key neurotransmitter receptors play a major role in determining the efficacy and adverse effect profile of each individual drug (see Table 1)<sup>8,9</sup>
- Ziprasidone, for example, exhibits relatively high dopamine D<sub>2</sub> occupancy at clinically recommended doses,<sup>10</sup> suggesting that a mechanism other than threshold D<sub>2</sub> receptor occupancy may account for its atypical profile.<sup>5</sup> This may be due to partial 5-HT<sub>1A</sub> agonism, which has been shown to enhance antipsychotic-like effects and reduce EPS in animal models<sup>11</sup>
- Aripiprazole has a different profile in being a *partial D<sub>2</sub> agonist*. Even high occupancy of D<sub>2</sub> receptors (>85%) does not induce EPS in humans<sup>12</sup>

## Therapeutic significance of blockade of other neurotransmitter receptors

• The atypical antipsychotics are a heterogeneous group that range from pure D<sub>2</sub> dopaminergic antagonists (e.g. amisulpride) to agents that act at multiple receptor sites, including serotonergic, muscarinic, histaminergic and alpha-adrenergic receptors (e.g. clozapine; see Table 1).<sup>1</sup> The receptors thought to contribute to the various side

effects of the antipsychotic medications are mentioned in the individual clinical sections of this data guide

• Most atypicals combine antagonist effects on the dopamine D<sub>2</sub> receptor family (D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub>) with potent antagonist effects on the 5-HT<sub>2A</sub> and adrenergic α<sub>1</sub> receptors.<sup>8</sup> It is hypothesized that this profile provides selectivity for the limbic system, which is demonstrated most markedly for sertindole<sup>8</sup>

Table 1. Relative neurotransmitter receptor potencies of selected antipsychotic agents at therapeutic doses (K<sub>i</sub> values, nM)<sup>9\*</sup>

| Agent                     | Dopamine<br>D <sub>2</sub> | Serotonin          |                    |                    |                   |                   |
|---------------------------|----------------------------|--------------------|--------------------|--------------------|-------------------|-------------------|
|                           |                            | 5-HT <sub>1A</sub> | 5-HT <sub>2A</sub> | 5-HT <sub>2C</sub> | 5-HT <sub>6</sub> | 5-HT <sub>7</sub> |
| Haloperidol               | 2.0                        | 1,600              | 300                | >10,000            | >10,000           | 4500              |
| Amisulpride <sup>‡</sup>  | 21                         | >10,000            | 2,000              | >10,000            | ND*               | ND*               |
| Aripiprazole <sup>§</sup> | 3.3                        | 5.6                | 35                 | 22                 | 570               | 10                |
| Clozapine                 | 180                        | 190                | 6.3                | 13                 | 9.1               | 16                |
| Olanzapine                | 63                         | 3,200              | 2.3                | 18                 | 5.6               | 54                |
| Quetiapine                | 720                        | 420                | 280                | 2,500              | 1400              | 580               |
| Risperidone               | 4.1                        | 430                | 0.4                | 76                 | 3000              | 0.98              |
| Sertindole                | 12                         | 350                | 0.1                | 1.5                | 0.74              | 11                |
| Ziprasidone               | 6.8                        | 5.5                | 2.1                | 6.5                | 37                | 1.2               |

<sup>‡</sup>Table adapted from Leysen JE, 2000<sup>9</sup>. <sup>§</sup>Amisulpride values taken from Schoemaker H et al, 1997<sup>14</sup> \*ND, no data available. <sup>§</sup>Aripiprazole values taken from the PDSP K<sub>i</sub> database (<http://pdsp.cwru.edu/pdsp.php>).<sup>15</sup>

- Clozapine has the most complex receptor profile of the atypicals. Partial agonist activity of this agent at the 5-HT<sub>1A</sub> receptor has been postulated to contribute to its efficacy against anxiety, depression and cognitive and negative symptoms, and may enhance functional antidopaminergic activity.<sup>5</sup> Partial muscarinic M<sub>1</sub> agonism and high M<sub>1</sub> efficacy of the main clozapine metabolite have also been implicated.<sup>13</sup> It is also hypothesized that potent 5-HT<sub>2A</sub> receptor and adrenergic  $\alpha_1$  receptor antagonism contribute to the profile of the atypical antipsychotics<sup>8</sup>
- Antipsychotics show large variation in their affinities for the 5-HT<sub>6</sub> and 5-HT<sub>7</sub> receptors. In particular, 5-HT<sub>6</sub> receptor antagonism has gained interest recently as a possible mediator of cognitive improvements.<sup>8,9</sup> Sertindole, clozapine and olanzapine exhibit the highest potencies for this receptor<sup>9</sup>

|  | Muscarinic<br>M | Adrenergic<br>$\alpha_1$ | Adrenergic<br>$\alpha_2$ | Histaminic<br>H <sub>1</sub> |
|--|-----------------|--------------------------|--------------------------|------------------------------|
|  | 3500            | 26                       | 1,000                    | 1,200                        |
|  | >100,000        | 7,100                    | 1,600                    | >10,000                      |
|  | 6,800           | 26                       | 74                       | 29                           |
|  | 33              | 22                       | 54                       | 1.1                          |
|  | 55              | 58                       | 430                      | 1.2                          |
|  | 1,100           | 52                       | 1,800                    | 8.3                          |
|  | >10,000         | 2.5                      | 21                       | 33                           |
|  | 2,400           | 2.0                      | 360                      | 490                          |
|  | 2,500           | 13                       | 190                      | 65                           |

# Effects of atypical antipsychotics on positive symptoms

- Positive psychotic symptoms of schizophrenia include:

- Psychomotor agitation
- Aggression
- Delusions
- Hallucinations
- Abnormal behaviour
- Abnormal thought content

These are particularly responsive to anti-psychotic treatment.<sup>3</sup>

Findings from meta-analyses concur that the atypicals exhibit at least equal efficacy compared with conventional antipsychotic agents, such as haloperidol<sup>16-18</sup>

- Conclusions from meta-analyses regarding efficacy between atypicals vary:
  - Geddes et al suggest no significant differences between atypicals in terms of positive symptoms<sup>16</sup>
  - Davis et al conclude that some atypicals (e.g. clozapine) are superior to others and suggest that clozapine dose is a significant variable in terms of efficacy<sup>18</sup>

- The multicentre US CATIE\* study revealed improvements in total PANSS<sup>5</sup> scores over time in all treatment groups (olanzapine, perphenazine, quetiapine, risperidone, ziprasidone) but significant variations in treatment effects over time ( $p=0.002$ ).<sup>19</sup> Olanzapine was associated with the greatest initial improvements, the greatest reductions in psychopathology and the longest duration of successful treatment, although its advantages diminished over time<sup>19</sup>
- Large, ongoing head-to-head comparisons will provide further information on comparable efficacy with the atypicals

# Effects of atypical antipsychotics on negative symptoms

- Negative symptoms (diminished emotional responses and spontaneity, social withdrawal/isolation, blunted mood expression, poverty of speech, lack of energy) are prominent features of schizophrenia that can result from disease pathology or antipsychotic medication<sup>2</sup>
- Data strongly suggest greater efficacy of atypicals versus typicals in the treatment of negative symptoms, although whether these effects are due to a direct improvement in negative symptoms or are secondary to a reduction in EPS and other side effects remains unclear<sup>5,18</sup>
- Studies comparing atypicals (sertindole, risperidone, olanzapine) with haloperidol have indicated that improved negative symptoms with atypicals could not be explained by effects on EPS and other symptoms alone, suggesting direct therapeutic effects<sup>20-22</sup>
- Studies comparing the atypicals have demonstrated varying efficacy of these agents against negative symptoms, assessed using PANSS<sup>§</sup> and SANS<sup>†</sup> scores (Table 2)

\*CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; <sup>§</sup>PANSS, Positive and Negative Syndrome Scale; <sup>†</sup>SANS, Scale for Assessment of Negative Symptoms

**Table 2. Efficacy of atypical antipsychotics against negative symptoms in clinical trials (presented in alphabetical order)**

| Comparison                                 | Study design  | Patient group  | N   | Outcome   | p-value |
|--|---|--|-----|---|---------|
| Amisulpride vs. risperidone <sup>23</sup>  | Double-blind, 8-weeks   | Patients with acute exacerbations of schizophrenia                   | 228 | Non-significant improvement in negative symptoms with amisulpride   | p=0.09  |
| Aripiprazole vs. risperidone <sup>24</sup> | Double-blind, 4-weeks   | Schizophrenia patients with acute exacerbations of positive symptoms | 404 | Comparable improvements in PANSS subscale scores                    | NS      |
| Olanzapine vs. risperidone <sup>25</sup>   | Double-blind, parallel-group, 28-weeks                            | Schizophrenia, schizophreniform disorder, schizoaffective disorder   | 339 | Significant improvement in SANS summary score with olanzapine       | p=0.02  |
| Risperidone vs. quetiapine <sup>26</sup>   | Randomized, open-label, 4-months                                  | Schizophrenia outpatients with broad range of symptoms               | 728 | No significant differences in PANSS subscales                       | NS      |
| Sertindole vs. risperidone <sup>27</sup>   | Randomized, double-blind, parallel-group, flexible-dose, 12 weeks | Paranoid, disorganized, catatonic or undifferentiated schizophrenia  | 186 | Significant improvement in negative subscale scores with sertindole | p<0.05  |

# Effects of atypical antipsychotics on cognitive symptoms

- Cognitive impairments occur commonly in schizophrenia and exert a considerable impact on patient quality of life, sociovocational functioning and outcomes through negative effects on attention, memory, executive function, motor skills and visuospatial ability<sup>2,3,28,29</sup>
- Typical antipsychotics do not improve cognition and may impair memory function due to strong antimuscarinic and antidopaminergic properties<sup>1,30</sup>
- In contrast, trials and meta-analyses suggest that atypicals confer cognitive improvements in the areas of learning, processing speed, verbal fluency and motor skills (Table 3)<sup>29,30</sup>
- It seems likely that cognitive enhancement may result from effects of the atypicals that are not shared with the typicals, such as:<sup>29</sup>
  - Increased release of dopamine and acetylcholine in the prefrontal cortex or hippocampus
  - Antagonism of the 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub> or 5-HT<sub>6</sub> receptors
  - Stimulation of the 5-HT<sub>1A</sub> receptors
- Improvements with atypicals may also be due, in part, to reduced incidence of EPS and reduced use of anticholinergic drugs compared with typical agents<sup>1</sup>
- Preliminary data suggest that no atypical is superior or inferior to another in terms of overall cognitive function but differences emerge in vigilance/attention and verbal fluency (Table 3).<sup>29</sup> A 1-year outpatient study, for example, showed greater benefits with olanzapine or risperidone than haloperidol but few differences between olanzapine and risperidone other than in terms of specific areas of cognitive function.<sup>31</sup> A short-term study in outpatients who were switched to ziprasidone from the atypicals olanzapine or risperidone revealed significant improvements in secondary verbal memory, vigilance and executive function with ziprasidone<sup>32</sup>
- Studies of cognitive performance with sertindole versus haloperidol and atypical agents have revealed benefits with sertindole. A comparison with haloperidol suggested the superiority of sertindole in terms of early and long-lasting improvements in reaction time and short-term memory recall and benefits over time in executive function.<sup>28</sup> Data from a novel animal model suggested that sertindole conferred benefits in cognitive function compared with haloperidol, clozapine and risperidone.<sup>33</sup> Haloperidol was ineffective while only trends towards nonsignificant improvements were seen with clozapine and risperidone<sup>33</sup>

Table 3. Effects of atypical antipsychotics on cognition

| Agent        | Effect on cognition  |
|--------------|--|
| Risperidone  | Minor improvements in attention, executive function, verbal learning, memory and working memory compared with haloperidol, possibly through antagonism of the 5-HT <sub>2A</sub> receptor. <sup>30,34</sup> Superior improvements in memory and verbal learning compared with clozapine, haloperidol or olanzapine. <sup>35</sup>  |
| Olanzapine   | Improvements in attention, executive function, verbal learning, memory and fluency comparable to those with clozapine. <sup>36</sup> Superior cognitive benefits relative to haloperidol and risperidone. <sup>37</sup> Clinically significant improvements in processing speed, attention, perceptual organization and executive capacity compared with clozapine, haloperidol or risperidone. <sup>35</sup> Superior to ziprasidone in terms of verbal fluency but comparable across other cognitive measures. <sup>38</sup> |
| Quetiapine   | Appears to exert positive impact on verbal reasoning, fluency, memory and attention when compared with haloperidol. <sup>39,40</sup>   |
| Ziprasidone  | At 6 weeks, significant improvements from baseline in attention, memory, working memory, motor speed and executive function that were comparable to those with olanzapine. <sup>38</sup> Benefits in outpatients switched to ziprasidone from the typicals olanzapine or risperidone in terms of secondary verbal memory, vigilance and executive function. <sup>32</sup>  |
| Sertindole   | Associated with significantly improved PANSS cognitive component score <sup>41</sup> and beneficial effects on reaction time, working memory and executive function compared with haloperidol. <sup>28</sup> Improvements in cognitive function compared with haloperidol, clozapine and risperidone in animals. <sup>33</sup>   |
| Aripiprazole | Stimulatory effects on dopamine release in the medial prefrontal cortex and hippocampus thought to improve cognition. <sup>42</sup> A 26-week study revealed similar (general cognitive function) or improved (verbal learning) neurocognitive function from baseline with aripiprazole compared with olanzapine. <sup>43</sup>  |
| Clozapine    | Associated with improvements in cognitive function compared with typicals, including verbal fluency, attention, psychomotor speed, memory and learning. <sup>44-47</sup> Improvements in motor performance compared with haloperidol, risperidone and olanzapine. <sup>35</sup>  |

# Anticholinergic activity

- A number of antipsychotics, and particularly clozapine and olanzapine, show high affinity for muscarinic cholinergic receptors in the brain (see Table 1).<sup>5,48,49</sup> Anticholinergic side effects of the antipsychotic agents can include delirium, acute confusion and dizziness and are frequently associated with cognitive impairment (i.e. memory impairment). Other anticholinergic side effects include dry mouth, blurred vision, urinary retention, impaired intestinal peristalsis and tachycardia<sup>50</sup>
- Such effects are exacerbated by reduced cholinergic activity in the central nervous system in elderly patients or those with dementia<sup>49,51</sup>
- Due to its anticholinergic activity, clozapine may impair intestinal peristalsis, resulting in a risk of adverse effects ranging from constipation to intestinal obstruction, faecal impaction and paralytic ileus<sup>52</sup>
- As a result of its receptor profile with low affinity for cholinergic and histaminergic receptors, sertindole has negligible potential to cause sedation and cognitive impairment<sup>53</sup>
- In addition to anticholinergic effects clozapine often induces a paradoxical response, hypersalivation. It has been observed that clozapine and its main metabolite have variable efficacies at muscarinic receptor subtypes, ranging from full agonism, to partial agonism and antagonism. M4 agonism has been proposed to be involved in salivation<sup>13,54</sup>

# Extrapyramidal side effects

## High incidence of EPS with conventional antipsychotics

- Approximately 50–75% of patients receiving typical antipsychotics experience EPS:<sup>2</sup>
  - Akathisia
  - Parkinsonism
  - Dystonia/tardive dystonia
  - Dyskinesia/tardive dyskinesia (TD)

- EPS are associated with distress, compromised function, increased risk of negative symptoms, cognitive impairment, poor outcomes and reduced compliance<sup>2</sup>

## Reducing the incidence of EPS with atypicals

- Atypicals are associated with a significantly lower risk of EPS than typical agents<sup>16</sup>
- EPS are caused by excessive dopamine D<sub>2</sub> blockade. The beneficial profile of atypical antipsychotics is believed to be due to additional effects on other neurotransmitter receptors (see pages 6–7)<sup>2,5,8</sup>

## Incidence of EPS with individual atypical agents

- Risk of EPS varies with antipsychotic agent, dose and neurological syndrome<sup>3</sup>
- Risperidone, olanzapine and ziprasidone lead to dose-related increases in EPS;<sup>2</sup> a risperidone dose of >10 mg/day causes a comparable incidence of EPS to haloperidol<sup>55</sup>
- In a recent meta-analysis, clozapine was the only atypical to show significantly fewer EPS than low-dose typical antipsychotics, although data were inconclusive for risperidone and quetiapine and lacking for ziprasidone and sertindole<sup>17</sup>
- In addition, clozapine confers a risk of potentially lethal agranulocytosis in 1% of patients (see page 22)<sup>7</sup>
- Data now suggest that sertindole, quetiapine, aripiprazole and clozapine, given within the therapeutic dose range, do not differ from placebo in terms of incidence of EPS (Table 4)<sup>2</sup>

Table 4. Relative risk of EPS with atypical antipsychotic agents<sup>3</sup>

| Antipsychotic agent | Risk of EPS |
|---------------------|-------------|
| Clozapine           | 0           |
| Quetiapine          | 0           |
| Sertindole          | 0           |
| Aripiprazole        | 0           |
| Olanzapine          | +           |
| Ziprasidone         | +           |
| Risperidone         | ++          |

- Sertindole confers significantly fewer EPS than haloperidol at all doses (8–24 mg/day)<sup>20</sup> and, in one study, was associated with EPS at placebo level<sup>56</sup>
- Reduced EPS may be associated with a reduced risk of suicide and improved patient compliance

### Specific adverse neurological effects

- Superiority of the atypicals over typical agents in the prevention of individual neurological effects (dyskinesias, akathisia, malignant syndrome) are unclear<sup>3</sup>
- Akathisia and the rare, but potentially fatal, malignant syndrome can occur with almost all antipsychotics, including clozapine<sup>3</sup>
- Studies have shown a lower incidence of TD with atypicals versus conventional agents<sup>3</sup>
- Recent findings suggest that in patients who have experienced problems with TD and other late-occurring movement effects, switching to sertindole may be effective in reducing such symptoms<sup>57</sup>

# Affective symptoms and suicide

- Depressive symptoms are common in schizophrenia. Syndromal depression ranges in prevalence from 25% to 60% in the clinical population<sup>2</sup>
- Suicide is the major premature cause of death among patients with schizophrenia<sup>2</sup>
- Studies suggest that the akathisia and similar side effects associated with typical antipsychotics are potentially significant risk factors for suicide<sup>2</sup>
- The potential link between fewer EPS and reduced suicide risk suggests a reduced rate of suicide with atypical antipsychotics in general<sup>2</sup>
- Data suggest that the atypicals show greater efficacy against suicidality than typical agents, although efficacy varies between agents. Comparisons of data from clinical trial databases suggest low rates of suicide with olanzapine and risperidone and, particularly, clozapine and sertindole<sup>2</sup>
- Differentiable effects on suicide amongst atypical antipsychotics has been speculated to be related to agent specific effects with regards to improving overall patient function, which is dependent on discernible improvements in psychotic symptoms and cognitive function, reduced depression, enhanced work and social function<sup>53</sup>

# Sedation and somnolence

- Sedation is a well-known side effect of conventional antipsychotic medications, mediated via effects on many receptor systems, particularly the histaminergic H<sub>1</sub> receptor<sup>1,2,50</sup>
- In addition, even pure D<sub>2</sub> receptor antagonists may exacerbate sedative effects leading to cognitive disturbances, such as attention deficits, although the two may not necessarily correlate<sup>2</sup>
- Somnolence is most prominent in the early treatment stages<sup>2</sup>
- Initial sedation may be useful in patients experiencing insomnia; however, long-term sedation can be distressing and potentially dangerous due to potential impairment of judgment, thinking and motor skills
- Data from US product labelling information suggest that somnolence is commonly reported in clinical trials of atypicals, occurring at an incidence of 5–39%, ranging from risperidone and aripiprazole with the lowest incidences to olanzapine and clozapine with the highest rates (Table 5).<sup>2</sup> Olanzapine, however, may cause both increased somnolence and sleep disturbance<sup>50</sup>
- Data suggest that low-dose amisulpride and sertindole are associated with low risks of somnolence.<sup>2</sup> Similar levels to placebo have been reported with sertindole, probably due to a low affinity for the histamine H<sub>1</sub> receptor<sup>2,58</sup>
- Patients receiving atypicals should be cautioned about performing activities requiring mental alertness. Clozapine and quetiapine, in particular, are associated with risks of somnolence, and concomitant use in conjunction with compounds that potentiate somnolence, such as alcohol, should be avoided

Table 5. Incidence of sedation associated with atypical agents from product labelling information<sup>2</sup>

| Sertindole   | No sedation       |
|--------------|-------------------|
| Amisulpride  | Mild sedation     |
| Aripiprazole | Mild sedation     |
| Risperidone  | Mild sedation     |
| Ziprasidone  | Mild sedation     |
| Olanzapine   | Moderate sedation |
| Quetiapine   | Moderate sedation |
| Clozapine    | Strong sedation   |

# Metabolic disorders: Weight gain, hyperglycaemia, lipids

- Weight gain can reduce patient compliance and increase the risks of heart disease, peripheral vascular disease and diabetes<sup>2,59</sup>
- Sedation, inactivity, specific factors associated with the psychiatric disorder and the effects of H<sub>1</sub> and 5-HT<sub>2c</sub> receptor blockade are risk factors for weight gain;<sup>3</sup> children are also at particular risk<sup>60</sup>
- Weight gain is a common adverse effect associated with atypical antipsychotics that is considered clinically significant if it exceeds 7% of initial weight<sup>2,3,59</sup>
- Data suggest significant variation in the risk of weight gain between atypicals<sup>2,61</sup>
  - Clozapine and olanzapine are associated with particularly high risks for weight gain, risperidone and sertindole confer intermediate risks, while amisulpride, aripiprazole and ziprasidone confer low risks of weight gain (Table 6)<sup>1-3,50,61,62</sup>

- In the EIRE study, 75% of patients receiving olanzapine listed weight gain as an adverse reaction, compared with 53% of those receiving risperidone and 40% of those prescribed haloperidol<sup>63</sup>
- Dietary adjustment and exercise are indicated, but may not be effective, for the prevention of weight gain

Table 6. Estimated weight increase after 10 weeks of treatment with atypical antipsychotics<sup>61</sup>

| Agent       | Mean increase in weight (kg) |
|-------------|------------------------------|
| Clozapine   | 4.45                         |
| Olanzapine  | 4.15                         |
| Sertindole  | 2.92                         |
| Risperidone | 2.10                         |
| Ziprasidone | 0.04                         |

- Some atypical antipsychotics may be associated with increased risks of hyperglycaemia and diabetes, with rates varying between agents<sup>3,52,62</sup>
- A trial assessing the effects of atypicals (clozapine, olanzapine, risperidone) and haloperidol on glucose and cholesterol levels in schizophrenia patients showed increased plasma glucose levels with clozapine, olanzapine and haloperidol, and increased cholesterol levels with clozapine and olanzapine<sup>64</sup>
- Data have shown 3.4 and 4.2 times greater risks of hyperlipidaemia and diabetes, respectively, with olanzapine than with typical agents, and 0.81 and 1.6 times greater risks of hyperlipidaemia and diabetes, respectively, with risperidone<sup>3</sup>
- Overall, evidence suggests that the risks of disturbances in glucose and lipid metabolism are greatest with clozapine and olanzapine, intermediate with quetiapine and risperidone, and lowest with aripiprazole and ziprasidone; however, available data are limited for aripiprazole and ziprasidone and show discrepancies for risperidone and quetiapine<sup>65</sup>
- Clinical experience with sertindole does not suggest an increased risk for diabetes. In short-term trials, only 4% of sertindole-treated patients displayed clinically significant increases in glucose values ( $\geq 175$  mg/dL) compared with 2% of placebo-treated patients<sup>2</sup>
- Many experts recommend regular glucose and lipid monitoring (every 6 or 12 months) in patients receiving antipsychotics<sup>59</sup>

# Prolactin elevation and sexual dysfunction

- Prolactin secretion is controlled by a complex mechanism, in which dopamine is the principal inhibitor<sup>62</sup>
- Two- to three-fold prolactin elevation can occur in patients receiving typical antipsychotics as a result of dopamine blockade, resulting in reduced gonadal hormone concentrations and a range of side effects:<sup>1,59,62</sup>
  - *In women*: menstrual disturbances, galactorrhea, breast engorgement, infertility, sexual dysfunction
  - *In men*: loss of libido, erectile dysfunction, gynaecomastia
  - *Long-term*: reduced bone density, cardiovascular disease, depression
- Hyperprolactinaemia occurs at a prevalence of 60% in women and 40% in men receiving typical agents or risperidone<sup>3</sup>
- Risperidone and amisulpride are associated with higher, dose-dependent occurrences of hyperprolactinaemia than other atypical agents, particularly aripiprazole and clozapine<sup>62</sup>
- Risperidone, in particular, is thought to increase prolactin levels more than typical agents and has been associated with higher levels of sexual dysfunction and decreased bone mineral density in premenopausal women than conventional and other atypical agents<sup>1,25,62</sup>
- Clozapine and quetiapine are associated with minimal prolactin elevation and olanzapine with transient increases due, in part, to interaction with receptors other than the dopaminergic receptor<sup>1,3,62</sup>
- Aripiprazole is a partial dopamine agonist, thus accounting for its negligible effects on prolactin secretion<sup>5</sup>
- Sertindole does not cause clinically significant increases in prolactin in short- and long-term (one year) studies

- Sexual dysfunction occurs frequently in patients with schizophrenia, particularly in men, and can develop as a result of the disease or its treatments<sup>66</sup>
- Sexual side effects can significantly affect patient compliance and are often the cause of considerable distress<sup>2</sup>
- A study of conventional antipsychotics reported an incidence of sexual dysfunction in men and women of 16–37%, including deficits in orgasm, erections and ejaculation<sup>67</sup>
- Sexual dysfunction occurs as a direct consequence of dopamine antagonism and through its effects on serum prolactin concentrations<sup>66,67</sup>
- Incidence of sexual dysfunction and effects on serum prolactin levels vary between atypicals, as mentioned in the previous section
- Incidence of sexual side effects with risperidone is comparable to that seen with typical agents. Clozapine and ziprasidone are associated with few sexual side effects, while men receiving sertindole are unaffected in terms of libido, erection or orgasm, experiencing only reduced ejaculatory volume<sup>53,58,66</sup>
- Risk of sexual dysfunction should be taken into account when considering appropriate treatment regimens<sup>66</sup>

# Agranulocytosis and other adverse use of clozapine

- Clozapine is a valuable treatment option for the management of patients with schizophrenia. However, unlike the other atypicals, clozapine is associated with the rare but serious side effect of agranulocytosis<sup>16</sup>
- Agranulocytosis can occur with clozapine use at an estimated incidence of 0.7–1% in patients who are not being closely monitored for leucocyte counts.<sup>3,52</sup> Patients are at greatest risk during the initial months of treatment<sup>3</sup>
- The incidence of agranulocytosis and associated mortality have decreased markedly since the introduction of strict leucocyte count monitoring in patients receiving antipsychotic treatment<sup>52</sup>

## **Incidence of other adverse effects with clozapine**

- Due to its activity at several receptor sites, clozapine is associated with a number of additional adverse events:
  - Increased risk of myocarditis ( $\leq 19/10,000$ ), particularly during the first 2 months of treatment; in rare cases this has been fatal<sup>3</sup>
  - Rare cases of fatal late cardiomyopathy ( $\leq 10/10,000$ )<sup>3</sup>
  - Dose-dependent risk of epileptic seizures (5% at a dose of 600 mg/day or more)<sup>3</sup>
  - Cerebral intoxication with fever and delirium (as seen with neuroleptic malignant syndrome)<sup>3</sup>
  - Orthostatic (postural) hypotension, particularly in elderly patients with compromised cardiovascular function<sup>50,52</sup>

# effects associated with the

Table 7. Preventing fatal agranulocytosis in patients receiving clozapine<sup>48,52</sup>

- A full blood test, history and physical examination should be taken before treatment initiation
- Patients with a history of cardiac illness or abnormal cardiac findings should be referred to a specialist for further examinations, including ECG
- Patients should only be treated if the benefits clearly outweigh the risks
- The use of clozapine should be limited to:
  - Patients with schizophrenia who are non-responsive or intolerant to antipsychotic treatments or with psychosis in Parkinson's disease in whom other treatments have failed
  - Patients with normal leucocyte counts on initiation ( $WBC^* \geq 3.5 \times 10^9/L$ ;  $ANC^y \geq 2.0 \times 10^9/L$ )
  - Patients in whom regular white blood cell and absolute neutrophil counts can be performed
- Physicians should pay particular attention to evidence of infection that may indicate neutropenia (fever, sore throat, flu-like symptoms)

\*WBC, white blood cell; <sup>y</sup>ANC, absolute neutrophil count

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September 2006

