

# Emerging role of sertindole in the management of schizophrenia

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**Abstract:** The atypical antipsychotic sertindole is a phenylindole-derived compound that has affinity for and functions as an antagonist at a number of receptor systems, including dopamine D2 receptors, 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors, and  $\alpha$ -1-noradrenergic receptors. Although previous data suggested that sertindole was well tolerated and had good efficacy against both positive and negative symptom clusters, reports of QT prolongation with sertindole prompted its voluntary removal from the market in 1998. After further safety analyses, it recently regained approval and was reintroduced to the European market for the treatment of schizophrenia, where its role in therapy among available atypicals remains unclear. This article evaluates the preclinical and clinical data regarding sertindole's effectiveness and concludes that sertindole continues to demonstrate a number of strengths, including effective management of both positive and negative symptoms, well-tolerated side effects (including little or no sedation, weight gain, and extrapyramidal side effects), and a superior procognitive profile that is unique among atypical antipsychotics. However, minor concerns regarding its sexual side effects and the major consideration of QT prolongation suggest that additional comparative effectiveness studies are needed to determine the superiority of sertindole vs other atypical antipsychotics recently introduced.

**Keywords:** atypical, antipsychotic, cognition, psychosis, 5-HT<sub>2</sub>, 5-HT<sub>6</sub>

## Introduction to management issues in the treatment of schizophrenia

Over the past 60 years, the environment surrounding the treatment of schizophrenia has changed dramatically. Historically, the treatment of the disease was managed in psychiatric institutions, where individuals were confined for much, if not all, of their lives. Following the introduction of the first antipsychotic medications (eg, chlorpromazine, haloperidol), however, treatment paradigms began to evolve from longer-term, in-patient treatment toward a system of managed outpatient care that is the current model of treatment regimens. At present, traditional and atypical antipsychotics remain the primary avenue of treatment for the disease and have demonstrated effectiveness in treating the presentation of both acute psychotic breaks and preventing relapse.<sup>1-3</sup> Moreover, atypical antipsychotics have the additional benefit of demonstrating remarkable efficacy against the negative symptom cluster of schizophrenia.<sup>4</sup>

However, it is clear that many problems still exist in terms of unmet needs in the pharmacological treatment of schizophrenia. First, there continues to be a large number of patients who demonstrate a poor response to treatment with antipsychotics.<sup>5,6</sup> A second issue associated with the use of these agents is their undesirable side-effect profiles that may impair both quality of life (eg, sedation, lethargy, sexual

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dysfunction) and physical health (eg, weight gain, obesity, hypertension).<sup>7</sup> A third arena of concern is the not infrequent development of extrapyramidal side effects (EPS), such as dystonia, Parkinsonism, and tardive dyskinesia, which occur more commonly after chronic treatment with traditional antipsychotic medications. In fact, tardive dyskinesia occurs in about one-fifth of patients with schizophrenia who are prescribed chronic regimens of first-generation agents<sup>8</sup> and is often associated with social stigmatization. Thus, the well-established, problematic side-effect profiles of both traditional and atypical antipsychotics make balancing the treatment of the disease against other negative health concerns, such as sedation, weight gain,<sup>9,10</sup> metabolic disorders,<sup>11,12</sup> and prolactin elevation,<sup>13,14</sup> challenging at best.

Recently, it has become evident that the long-term treatment of schizophrenia is compounded by significant impairment in cognitive domains. Although this would seem to be a more recent observation, even Kraepelin's initial characterization of schizophrenia from over a century ago included descriptions of cognitive deficits,<sup>15</sup> and these perspectives have gained greater attention in the more recent treatment literature.<sup>16,17</sup> Cognitive deficits observed in patients with schizophrenia appear widespread and are related to executive function, working memory, and attention. These cognitive deficits are present at the onset of illness, persist for most of patients' lives without remission, and may precede the development of positive symptoms.<sup>18,19</sup> Unlike psychotic symptoms, cognitive deficits demonstrate a robust inverse association with community functioning and illness outcome.<sup>20–22</sup> Therefore, treatments that attenuate cognitive deficits have the potential to significantly improve patients' quality of life.

Conventional antipsychotic treatments (eg, haloperidol) are reported not only to lack effect on cognitive deficits<sup>23</sup> but also to impair some cognitive functions.<sup>24,25</sup> Novel antipsychotic compounds (second-generation or "atypical" antipsychotics), such as clozapine,<sup>26</sup> olanzapine,<sup>27</sup> and sertindole,<sup>28,29</sup> have demonstrated some beneficial effects on negative symptoms and reduced potential to produce EPS, but these agents have demonstrated inconsistent effects on cognitive function in patients with schizophrenia. Depending on the type of cognitive domain measured, second-generation atypical antipsychotics have been reported to produce improvement,<sup>23,30,31</sup> no effect,<sup>30,32</sup> and impairment.<sup>33</sup> Thus, finding effective treatments that manage both positive and negative symptoms while also having the capacity to address cognitive dysfunction would seem to be the key.

A final aspect for consideration in the management of schizophrenia is the total costs incurred due to disease. Certainly, schizophrenia places a heavy burden on society because of the large demand on the health care infrastructure but just as important is the burden placed on families and caretakers. Schizophrenia, long considered the most chronic, debilitating, and costly mental illness, now consumes a total of about US\$63 billion a year for direct treatment, societal, and family costs.<sup>34</sup> Schizophrenia accounts for a fourth of all mental health costs and takes up 1 in 3 psychiatric hospital beds.<sup>34</sup> To the effect that only 10%–15% of people with schizophrenia are able to maintain full-time employment of any type,<sup>34</sup> public assistance assumes the cost of living. In 2002, the total direct nonhealth care excess costs in the United States, including living cost offsets, were estimated to be US\$7.6 billion with indirect excess costs (primarily due to un- and under-employment) of US\$32.4 billion.<sup>34</sup> Thus, schizophrenia is a debilitating illness resulting in significant costs that must be considered in a discussion of emerging treatments.

## Risks and benefits in use of sertindole

Sertindole, manufactured by H Lundbeck A/S (Copenhagen, Denmark), is an atypical antipsychotic that has proven clinical efficacy in the treatment of schizophrenia psychosis and also improves negative symptoms without producing EPS, when compared with traditional antipsychotics.<sup>35,36</sup> Previous work has demonstrated that striatal D2 occupancy is a predictive measure of antipsychotic clinical efficacy<sup>37,38</sup> and also suggests that antipsychotic efficacy is not associated with a high degree of striatal D2 receptor occupancy in schizophrenia.<sup>39</sup>

After introduction of sertindole to the European market in 1996, concerns regarding an association with prolonged QT intervals, possibly related to fatal ventricular arrhythmias including Torsade de Pointes (TdP), led to its voluntary withdrawal from the market in December 1998. Because of these apparent risks, a number of studies were undertaken to investigate sudden death claims related to sertindole, yet none of the studies thus far have been able to confirm that sertindole conveys an increased risk of sudden death.<sup>40–44</sup> As such, sertindole was re-released and was made available in the European market for prescriptions beginning in 2006 with the stipulation of close electrocardiogram (ECG) screening and monitoring. Further studies have shown that sertindole has a low arrhythmogenic potential and is not associated

with a rate of cardiovascular mortality higher than other antipsychotic agents.<sup>44</sup>

## Pharmacology, mode of action, and pharmacokinetics of sertindole

Sertindole is phenylindole-derived compound that is classified as a second-generation, or atypical, antipsychotic medication. It has affinity for and functions as an antagonist at a number of receptor systems, including dopamine D<sub>2</sub> receptors, 5-HT<sub>2</sub> receptors (particularly 2A and 2C subtypes), and  $\alpha$ -1-noradrenergic receptors.<sup>45</sup> Antagonism of these receptor systems are hypothesized to be involved in the antipsychotic effectiveness.<sup>46</sup> Like other atypicals, sertindole has selective effects on the dopaminergic system, affecting the mesocorticolimbic rather than mesostriatal neurons.<sup>45,47</sup> Previous data have implicated a number of atypical antipsychotics, including risperidone, sertindole, and ziprasidone, in QT prolongation.<sup>48–50</sup> An extended discussion of sertindole clinical pharmacokinetics is beyond the scope of this review (for a review of antipsychotic clinical pharmacokinetics, see Mauri et al<sup>51</sup>), but we will briefly address the issues of arrhythmias and metabolism/pharmacokinetics.

When concern was raised over the potential for sertindole to provoke fatal arrhythmias, the cardiac effects of sertindole were investigated in several preclinical and clinical studies.<sup>52–54</sup> Most antipsychotic agents have been demonstrated to show electrophysiological effects resembling those of antiarrhythmic agents, and indeed may be responsible for QT-interval prolongation.<sup>55</sup> Sertindole was ranked as the new atypical agent having the greatest risk of producing QT-interval prolongation, followed by ziprasidone and risperidone (both producing moderate risk) with the atypical compounds clozapine, olanzapine, and quetiapine deemed to have no effects on QT intervals.<sup>56</sup> In healthy dogs, sertindole exposure was not associated with the development of TdP, but in dogs with chronic atrioventricular block, high intravenous doses of sertindole were able to induce TdP.<sup>57</sup> The proarrhythmic effect of sertindole was subsequently compared with sotalol, a class III antiarrhythmic with inhibitory effects on potassium ion channels and  $\beta$ -adrenergic receptors.<sup>58</sup> The QTc effects of sotalol and sertindole were comparable, but at low potassium levels sotalol elicited TdP, whereas sertindole only elicited monomorphic tachycardia and nonsustained polymorphic tachycardia. This difference has been attributed to sertindole's concurrent inhibitory effects on sodium and calcium influx channels,<sup>59</sup> as well as to its  $\alpha$ -1-adrenoceptor blockade, whereby a reflex sinus tachycardia may protect against the development of TdP specifically. Sertindole also has a low ratio

of myocardium/plasma distribution; thus, this limited distribution to the myocardium may decrease the effective concentration at rapid delayed rectifier K<sup>+</sup> channels (I<sub>Kr</sub> sites).<sup>60</sup>

Excessive weight gain is a common side effect of some, but not all, typical and atypical antipsychotic medications, with clozapine and olanzapine being the antipsychotic medications with the greatest likelihood of inducing weight gain (for reviews, see Baptista et al<sup>61</sup> and Spina and de Leon<sup>62</sup>). Sertindole treatment engenders relatively moderate weight gain that is comparable to risperidone, but greater than ziprasidone, amisulpride, haloperidol, fluphenazine, pimozide, and molindone. Notably, sertindole produces less weight gain than many antipsychotics, including clozapine, olanzapine, quetiapine, zotepine, chlorpromazine, and thioridazine.<sup>61</sup> Given the various mechanisms of action for sertindole, any weight gain observed in patients may result either from increased appetite due to drug interactions with cholinergic and monoaminergic systems or perhaps from hyperprolactinemia. In addition, one problematic issue with the treatment of schizophrenia is that polypharmacy (or drug “cocktails”) might be used in treatment regimens, and as such, additive weight gain effects resulting from treatment with multiple antipsychotics might be observed.

The introduction of the atypical antipsychotics in the treatment of schizophrenia coincided with an increased awareness of the potential for drug–drug interactions, particularly involving the cytochrome P450 (CYP) enzymes. When considering drug–drug interactions, it is useful to anchor any comparisons against clozapine, which is often considered the standard of the atypical agents. Clozapine has a rather complex pharmacokinetic profile, with large interpatient variability and many drug interactions.<sup>63</sup> In contrast, olanzapine presents as a medication with a very low incidence of drug interactions, largely as a result of requiring exceedingly high inhibition of CYP450 systems.<sup>64</sup> The results of both *in vivo*<sup>65</sup> and *in vitro*<sup>66</sup> experiments suggest that the metabolism of sertindole is principally mediated by CYP3A4 and CYP2D6, and the known variability of these 2 isoenzymes likely contributes to the observed variability in the pharmacokinetics of sertindole.<sup>67</sup> In addition, the inhibitory potential of sertindole at CYP2A,<sup>68</sup> CYP2D6, and CYP3A4<sup>69</sup> is relatively modest and not likely to be of any clinical significance in any patients, except for those already taking CYP2D6 inhibitors or those who are poor metabolizers. In contrast, sertindole was observed to produce direct inhibitory effects on CYP2B<sup>68</sup> and CYP2C6 activities *in vitro*.<sup>70</sup>

Sertindole is relatively well absorbed when administered orally, penetrates the blood–brain barrier well and is largely

bound (99.5%) to plasma proteins. At doses of 4–32 mg/d, the  $T_{max}$  is 8–12 hours and the terminal elimination half-life ranges from 50 to 111 hours.<sup>67</sup> The mean elimination half-life of sertindole is about  $70 \pm 60$  hours, with an oral clearance of  $40 \pm 31$  L/h.<sup>71</sup> The mean  $C_{max}$  of sertindole was 2 ng/mL after the first dose and 10 ng/mL after the seventh dose.<sup>72</sup> Given these data, it is not surprising that significant sertindole accumulation can occur during multiple dosing. Dosing with 12 mg/d and 20 mg/d can produce steady-state levels after about 9 and 5 days, respectively.<sup>71</sup>

Sertindole is metabolized into major (Lu 30-131, 5-hydroxy-sertindole; Lu 30-148, 4-hydroxy-sertindole) and minor (Lu-25-073, norsertindole; Lu 28-092 dehydrosertindole; Lu 30-131, 5-hydroxy-sertindole) metabolites,<sup>73</sup> and none of these metabolites are reported to demonstrate any therapeutic effect. Moreover, sertindole pharmacokinetics do not seem to be significantly affected by age, sex, or race/ethnicity.<sup>74</sup> Because of metabolism pathway considerations, concurrent administration of CYP inhibitors, such as fluoxetine or paroxetine, is cautioned as these will likely increase plasma sertindole concentrations, whereas CYP inducers, such as carbamazepine or phenytoin, will decrease them. Additional care is needed when calculating effective doses in patients with hepatic insufficiency. The pharmacokinetics of sertindole are unchanged by renal impairment and deficiency, thus no dose adjustment is necessary in subjects diagnosed with renal insufficiency or in subjects with renal failure requiring dialysis treatment.<sup>73</sup> The main excretion pathway for sertindole is via feces and is observed across species.<sup>65</sup>

## Efficacy

The therapeutic efficacy of sertindole in patients with schizophrenia has been evaluated in 1 flexible-dose direct comparison with placebo, 3 efficacy comparisons with haloperidol, and 2 randomized controlled trials (RCTs) vs risperidone (see Table 1). Smaller retrospective and observational reports are available and will only briefly be noted here.

In a placebo-controlled, dose-ranging study of sertindole (8, 12, and 20 mg/d) in 153 patients with schizophrenia, use of sertindole 20 mg/d was associated with significantly greater improvements from baseline in the Clinical Global Impression (CGI) scale as well as in the Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) total scores, relative to placebo after 40 days.<sup>36</sup> Although the 8-mg/d dose was associated with numerically greater reductions on the PANSS and BPRS total scores, the difference was not significant. This study, therefore, suggested a dose-response relationship between sertindole

and improvement in psychiatric rating scales and established 20 mg/d as an effective, well-tolerated dose.

Data from 3 randomized trials suggest that sertindole is at least as effective as haloperidol in the treatment of schizophrenia and may be more effective in treating negative symptoms specifically. In a double-blind, placebo-controlled, dose-ranging trial of sertindole (12, 20, and 24 mg/d) and haloperidol (4, 8, and 16 mg/d) in 497 hospitalized patients with schizophrenia, both sertindole and haloperidol were associated with significantly greater improvements at all doses on PANSS and BPRS total scores compared with placebo.<sup>75</sup> A significant reduction was also noted in the CGI scale relative to placebo with all doses of sertindole and all but the 4-mg/d dose of haloperidol. All doses of haloperidol and only the 20- and 24-mg/d doses of sertindole were associated with significant reductions in the positive syndrome subscale of the PANSS. Interestingly, only the 20-mg/d dose of sertindole was significantly superior to placebo in improving negative symptoms as measured on the PANSS subscale and Scale for the Assessment of Negative Symptoms (SANS) over the course of the study. In a longer-term, randomized study of sertindole (24 mg/d) vs haloperidol (10 mg/d) in 282 outpatients with schizophrenia, sertindole was associated with a significantly greater reduction in the SANS total score from baseline after 2 months of treatment; however, there was no significant difference between the 2 treatment groups after 12 months.<sup>76</sup> In another double-blind, randomized, dose-ranging study of sertindole (8, 16, 20, and 24 mg/d) vs haloperidol (10 mg/d) in 617 patients with schizophrenia, sertindole (16 mg/d) demonstrated significantly greater improvement on the negative subscale of the PANSS compared with haloperidol (10 mg/d).<sup>77</sup> Increasing the dose of sertindole to 20–24 mg/d revealed no greater benefit in terms of either PANSS total or negative subscale scores. There were no significant differences between sertindole (16–24 mg/d) and haloperidol (10 mg/d) on PANSS total score improvement.

Direct comparisons of sertindole with second-generation antipsychotic drugs are lacking and are currently limited to two 12-week RCTs with risperidone, and these analyses are limited themselves by early study termination upon withdrawal of the drug from the market. A randomized, double-blind study initially revealed superior efficacy of sertindole (12–24 mg/d) over risperidone (4–10 mg/d) on both PANSS total and negative symptom subscale scores in 186 patients with schizophrenia.<sup>29</sup> A subsequent randomized, double-blind study comparing sertindole (12–24 mg/d) with risperidone (6–12 mg/d) in 217 treatment-resistant (defined as

**Table 1** Efficacy studies of SER vs PL, HAL, and RIS

| Reference                      | Treatment length (wk) | Drug and dose (mg/d) | No. (ITT analysis) | Efficacy measure (mean decrease from baseline to final assessment) |                    |                     |                     |                    |                     |
|--------------------------------|-----------------------|----------------------|--------------------|--|--------------------|---------------------|---------------------|--------------------|---------------------|
|                                |                       |                      |                    | PANSS total  | PANSS positive     | PANSS negative      | BPRS                | CGI <sup>a</sup>   | SANS                |
| <b>vs placebo</b>              |                       |                      |                    |  |                    |                     |                     |                    |                     |
| van Kammen et al <sup>36</sup> | 6–7                   | SER 8                | 35                 | 5.0  | 1.6                | 0.2                 | 4.4                 | 4.0                |                     |
|                                |                       | SER 12               | 40                 | 12.1   | 3.0                | 2.1                 | 8.0                 | 3.5                |                     |
|                                |                       | SER 20               | 40                 | 16.9*  | 3.5                | 3.0                 | 10.4*               | 2.9*               |                     |
|                                |                       | PL                   | 38                 | 5.8  | 1.6                | 1.3                 | 4.8                 | 3.8                |                     |
| <b>vs haloperidol</b>          |                       |                      |                    |  |                    |                     |                     |                    |                     |
| Zimbroff et al <sup>75</sup>   | 8                     | SER 12               | 72                 | 10.0 <sup>b**</sup>  | 2.4                | 2.5 <sup>b</sup>    | 6.7 <sup>**</sup>   | 3.5 <sup>**</sup>  | 7.9*                |
|                                |                       | SER 20               | 65                 | 17.6 <sup>b***</sup>   | 4.8 <sup>***</sup> | 4.3 <sup>b***</sup> | 10.3 <sup>***</sup> | 3.3 <sup>**</sup>  | 13.2 <sup>***</sup> |
|                                |                       | SER 24               | 70                 | 10.8 <sup>b**</sup>  | 3.2 <sup>*</sup>   | 2.2 <sup>b</sup>    | 8.2 <sup>**</sup>   | 3.6 <sup>**</sup>  | 7.1                 |
|                                |                       | HAL 4                | 68                 | 11.8 <sup>b**</sup>  | 2.7 <sup>*</sup>   | 2.5 <sup>b</sup>    | 8.0 <sup>**</sup>   | 3.7                | 10.9                |
|                                |                       | HAL 8                | 63                 | 16.5 <sup>b***</sup>   | 5.6 <sup>***</sup> | 3.3 <sup>b</sup>    | 10.4 <sup>***</sup> | 3.1 <sup>***</sup> | 10.8                |
|                                |                       | HAL 16               | 68                 | 12.2 <sup>b**</sup>  | 4.3 <sup>***</sup> | 2.2 <sup>b</sup>    | 8.8 <sup>**</sup>   | 3.5 <sup>*</sup>   | 7.1                 |
|                                |                       | PL                   | 71                 | −0.8 <sup>b</sup>  | 0.0                | 0.7 <sup>b</sup>    | 0.9                 | 4.2                | 2.1                 |
| Daniel et al <sup>76</sup>     | 52                    | SER 24               | 94                 | 5.8  |                    |                     |                     |                    | 3.9                 |
|                                |                       | HAL 10               | 109                | 1.4  |                    |                     |                     |                    | 0.1                 |
| Hale et al <sup>77</sup>       | 8                     | SER 8                | 116                | 16.2   | 4.6                | 4.2                 |                     | 3.1                |                     |
|                                |                       | SER 16               | 120                | 23.8 <sup>†</sup>  | 6.9 <sup>†</sup>   | 5.7                 |                     | 3.0                |                     |
|                                |                       | SER 20               | 121                | 20.1   | 6.3                | 4.9                 |                     | 3.1                |                     |
|                                |                       | SER 24               | 115                | 23.1 <sup>†</sup>  | 7.6 <sup>†</sup>   | 4.8                 |                     | 3.0                |                     |
|                                |                       | HAL 10               | 123                | 22.8 <sup>†</sup>  | 7.9 <sup>†</sup>   | 4.3                 |                     | 3.0                |                     |
| <b>vs risperidone</b>          |                       |                      |                    |  |                    |                     |                     |                    |                     |
| Azorin et al <sup>29</sup>     | 12                    | SER 12–24            | 90                 | 29.3   | 8.0                | 7.7 <sup>‡</sup>    |                     | 1.4 <sup>c</sup>   |                     |
|                                |                       | RIS 4–10             | 82                 | 25.8   | 7.2                | 6.4                 |                     | 1.3 <sup>c</sup>   |                     |
| Kane et al <sup>78</sup>       | 12                    | SER 12–24            | 213                | 12.0   | 3.3                | 2.5                 | 7.0                 | 0.5 <sup>c</sup>   | 7.5                 |
|                                |                       | RIS 6–12             | 102                | 19.0   | 5.8                | 3.7                 | 10.9                | 0.8 <sup>c</sup>   | 10.3                |

**Notes:** <sup>a</sup>CGI value is mean actual score on CGI improvement scale at final assessment (1, very much improved; 4, no improvement; 7, very much worse).

<sup>b</sup>Values estimated from a graph; as estimated by Murdoch and Keating.<sup>84</sup>

<sup>c</sup>Mean decrease on CGI-S (severity scale) from baseline to final assessment.

\* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$  vs placebo; <sup>†</sup> $P \leq 0.05$  vs SER 8 mg/d; <sup>‡</sup> $P \leq 0.05$  vs RIS 6–12 mg/d.

**Abbreviations:** SER, sertindole; PL, placebo; HAL, haloperidol; RIS, risperidone; ITT, intention to treat; PANSS, positive and negative syndrome scale; BPRS, brief psychiatric rating scale; CGI, clinical global impression; SANS, scale for the assessment of negative symptoms.

failure of adequate trials of  $\geq 2$  antipsychotic agents) patients with schizophrenia, however, demonstrated no significant differences in the same efficacy measures from baseline to final assessment.<sup>78</sup> A recent Cochrane review of pooled RCT data similarly revealed no difference in efficacy between these 2 antipsychotic drugs.<sup>79</sup> Sertindole, therefore, appears at least as effective as high-dose risperidone, however, its efficacy vs other atypical agents remains unclear.

Two small observational studies have reported significant improvement from baseline in patients treated with sertindole. In a naturalistic study of 53 patients with psychotic disorders prescribed sertindole (8–24 mg/d) before its withdrawal from the market, improvement in global assessment of functioning (GAF) and CGI scores between admission and discharge was highly significant ( $P < 0.001$ ).<sup>80</sup> Another smaller observational study of 34 patients with psychotic disorders reported an 85% response rate (defined as achieving a CGI score  $\leq 3$ ) with sertindole use initiated in the inpatient setting.<sup>42</sup> In summary,

both real-world and clinical research data support the efficacy of sertindole in the treatment of patients with schizophrenia (and to a lesser extent other psychotic disorders), although current evidence for its efficacy is limited to comparisons with placebo, haloperidol, and risperidone.

## Safety and tolerability

### QT prolongation

The association between sertindole use and QT prolongation has been demonstrated since its introduction to the European market, when clinical trials first documented a 20-millisecond heart rate corrected QT interval increase with sertindole use.<sup>81</sup> Shortly thereafter, the proportion of fatal cardiac arrhythmias and sudden deaths associated with sertindole (7.5%) were found to outnumber almost 10-fold those of either risperidone (0.8%) or olanzapine (0.9%) on the Adverse Drug Reactions Online Information Tracking (ADROIT) database, a regulatory monitoring system in the United Kingdom for

physician reports of adverse drug reactions.<sup>40</sup> These data prompted the manufacturer, Lundbeck Pharmaceuticals, to withdraw sertindole voluntarily from the market and conduct further studies to confirm the ADROIT data. Five subsequent epidemiological studies taken together established that sertindole was associated with no greater risk of death or serious cardiac adverse drug reaction than other second-generation antipsychotic drugs,<sup>40,43,44,82,83</sup> however, adverse drug reactions associated with sertindole were determined to be more frequently reported than those of other atypical agents.<sup>41</sup>

In 2002, the European Committee for Proprietary Medicinal Products decided to reintroduce sertindole to the European market with the stipulation that all sertindole-treated patients were to be included in a postmarketing surveillance study.<sup>84</sup> Data from that cohort, the Sertindole Cohort Prospective (SCoP) study, failed to determine any overall difference in all-cause mortality rates compared with treatment with risperidone; however, significantly more patients treated with sertindole died from an event considered possibly cardiac (ie, there was no evidence of a noncardiac cause) than those given risperidone.<sup>85</sup> Another study conducted under the named patient use program after sertindole's suspension, the Sertindole Safety Survey, retrospectively analyzed the serious adverse events (SAEs) reported among 1,432 patients treated with sertindole in 11 European countries.<sup>86</sup> Of the 97 SAEs identified, 10 had fatal outcomes (2 suicides, 3 sudden deaths [2 myocardial infarctions and 1 pulmonary embolism], 4 "other" deaths, and 1 unascertained cause of death). Of the 87 remaining nonfatal SAEs, 24 were considered cardiac in origin (15 cases of QT prolongation, 4 heart rate anomalies, 3 cardiac failures, 1 abnormal ECG, and 1 myocardial infarction).

The association between sertindole and QT prolongation remains robust, with industry-sponsored retrospective analysis replicating the increase of  $20 \pm 26$  millisecond in sertindole-treated patients ( $n = 160$ ) vs a decrease of  $5 \pm 22$  millisecond among controls ( $n = 162$ ) (from Lundbeck data).<sup>87</sup> A smaller, noncontrolled trial of 21 patients with schizophrenia treated with an average dose of  $14.7 \pm 4.6$  mg/d of sertindole found a significant increase in mean QTc interval from  $387.7 \pm 19.2$  millisecond at baseline to  $402.8 \pm 23.8$  millisecond after 6 months.<sup>88</sup> Of course, sertindole is not unique amongst its class in its propensity to prolong the QTc interval; olanzapine (1.7 millisecond at 20 mg/d), risperidone (3.6 millisecond at 16 mg/d), quetiapine (5.7 millisecond at 750 mg/d), and ziprasidone (15.9 millisecond at 160 mg/d) have all been documented to lengthen the QTc interval, albeit not more than the first-generation neuroleptic thioridazine (30.1 millisecond at 300 mg/d).<sup>89</sup> Independent of its

association with QT prolongation,<sup>90,91</sup> however, sertindole has also been shown to induce T wave morphologic changes (flatness, asymmetry, or notches) in a majority (26 of 37 patients) of patients in one study, suggesting that patients predisposed to arrhythmias or even sudden cardiac death may be missed if patients are only screened for QT prolongation.<sup>92</sup> In summary, sertindole is associated with a prolongation of the QT interval that has not been linked to the development of cardiac arrhythmias, however, further evidence will be helpful in elucidating the impact, if any, of its electrophysiological profile on cardiac-related mortality.

## Extrapyramidal symptoms

The reduced incidence of EPS associated with second-generation antipsychotic drugs has been attributed to their limbic preferentiality and decreased striatal dopamine D2 receptor occupancy relative to their typical counterparts. In following, available data suggest that sertindole may be associated with a lower incidence of EPS compared with haloperidol and risperidone. In a double-blind, controlled study of sertindole vs risperidone, patients treated with sertindole (at a mean dose of 16.2 mg/d) experienced numerically fewer EPS-related treatment-emergent adverse events than those given risperidone (6.6 mg/d; 19% vs 28%).<sup>29</sup> More recently, another double-blind, randomized study comparing sertindole (12–24 mg/d) with risperidone (6–12 mg/d) revealed a significantly lower incidence of EPS among sertindole-treated patients (20.8% vs 36.2%,  $P < 0.01$ ).<sup>78</sup> Unsurprisingly, sertindole (24 mg/d) has been associated with a significantly lower incidence of EPS-related adverse events relative to haloperidol (4–16 mg/d) after 8 weeks of treatment (23.6% vs 43.7%–55.7%), with rates indistinguishable from placebo (27.4%).<sup>75</sup> A long-term efficacy trial of sertindole similarly revealed a 17% lower incidence of EPS associated with sertindole (24 mg/d) compared with haloperidol (10 mg/d).<sup>76</sup> Importantly, the emergence of EPS with sertindole use does not appear to be dose-dependent,<sup>36</sup> whereas the incidence of EPS with olanzapine and risperidone has been found to increase with higher doses.<sup>54</sup>

Although the incidence of EPS with sertindole may appear exceptionally low, there is currently no data comparing the risk of EPS between sertindole and other atypical antipsychotics with lower dopamine D2 receptor affinity than risperidone. In conjunction with its low risk of EPS, however, sertindole may have a role in treating patients with undesirable movement disorders associated with the use of conventional neuroleptics. In one case series of 4 patients with tardive dystonia, dyskinesia, or akathisia, switching from a

first-generation antipsychotic drug to sertindole considerably improved both the movement disorder and the severity of psychotic symptoms,<sup>93</sup> although this effect has been noted with olanzapine, quetiapine, and clozapine as well.<sup>94</sup>

## Metabolic profile and weight

The prevalence of metabolic syndrome among patients with schizophrenia now doubles that of the general population, conferring tremendous risk of diabetes and heart disease most notably to those treated with second-generation antipsychotic drugs.<sup>95</sup> Limiting the risk of metabolic syndrome has accordingly become a priority within both clinical practice and drug development. In a subset of 261 patients with schizophrenia randomized to receive either sertindole or risperidone, neither treatment was associated with an increased risk of metabolic syndrome from baseline to last assessment, spanning up to 12 months.<sup>96</sup> However, both sertindole and risperidone use were associated with an increase in weight (1.8 and 1.7 kg, respectively), waist circumference (1.4 and 1.5 cm, respectively), and body mass index (0.6 and 0.6 kg/m<sup>2</sup>, respectively). Placebo-controlled trials have noted similar, small but significant weight increases with sertindole vs placebo use, with weight gain ranging from 2.2 to 3.3 kg over 40–56 days of treatment.<sup>36,75</sup> Double-blind trials of sertindole vs risperidone also reported a 2.1- to 3.1-kg weight gain with sertindole, which did not differ significantly from that of risperidone (1.5–2.5 kg) over 12 weeks.<sup>29,78</sup> Treatment with sertindole has also been associated with small increases in plasma glucose,<sup>78,96</sup> total cholesterol,<sup>36,78</sup> and triglycerides,<sup>78</sup> although most studies report negative results on these parameters.

## Other treatment-emergent adverse events

Both placebo-controlled and randomized, controlled comparator trials with sertindole suggest that it is well tolerated among patients with schizophrenia. Adverse event reporting from 6 trials (see Table 2) suggests that sertindole is most commonly associated with rhinitis/nasal congestion (15.3%–34.7%), nausea (11.0%–13.0%), abnormal ejaculation (8.9%–21.8%), insomnia (9.3%–31.3%), somnolence (8.2%–18.1%), and headache (5.2%–33.8%). Interestingly, the only adverse event reported in all 6 trials was abnormal ejaculation, including both decreased ejaculatory volume and absence of ejaculation. The ejaculatory abnormalities associated with sertindole use may stem from its  $\alpha$ -1-adrenoreceptor antagonist activity,<sup>35</sup> which has been linked to ejaculatory dysfunction with risperidone<sup>97</sup> and thioridazine<sup>98</sup> use, although this remains speculative.

**Table 2** Most frequent adverse events reported in patients treated with sertindole,<sup>a</sup> % by study

| Event                             | Kane et al <sup>78</sup> | Azorin et al <sup>79</sup> | Steinert et al <sup>80</sup> | Serdolect™ monograph data (Perquin and Steinert <sup>35</sup> ) | Zimbroff et al <sup>75</sup> | van Kammen et al <sup>86</sup> |
|-----------------------------------|--------------------------|----------------------------|------------------------------|---|------------------------------|--------------------------------|
| Weight gain                       | n = 217                  | n = 187                    | n = 53                       | n = 2,454   | n = 216 <sup>b</sup>         | n = 157 <sup>b</sup>           |
| Headache                          | 29.2                     | 20.6                       | 5                            | 33.8  |                              | 28.0                           |
| Anxiety                           |                          | 5.2                        |                              |   |                              |                                |
| Insomnia                          | 18.1                     | 18.6                       |                              | 31.3  |                              | 17.8                           |
| Vomiting                          | 17.1                     | 9.3                        |                              |   |                              |                                |
| Dyspepsia                         | 15.7                     |                            |                              | 13.7  |                              | 8.9                            |
| Rhinitis/congestion               | 15.3                     |                            | 16                           | 28.5  | 34.7                         | 19.1                           |
| Abnormal ejaculation (% men only) | 14.8                     | 18.5                       | 14                           | 21.8  | 12.0                         | 8.9                            |
| Nausea                            | 13.0                     |                            |                              | 11.0  | 12.5                         |                                |
| Somnolence                        | 11.6                     | 8.2                        |                              | 18.1  | 15.3                         | 8.9                            |
| Infection                         |                          |                            |                              | 16.8  |                              | 10.2                           |
| Dizziness                         | 10.6                     |                            |                              | 14.8  |                              | 7.6                            |
| Constipation                      |                          | 7.2                        | 7                            | 13.2  |                              | 10.8                           |
| Asthenia                          |                          | 7.2                        |                              | 14.6  |                              |                                |
| Myalgia                           |                          |                            |                              | 12.0  |                              |                                |
| Increased thirst                  |                          |                            | 16                           |   |                              |                                |
| Dry mouth                         |                          |                            |                              | 11.9  |                              |                                |
| Depression                        |                          |                            |                              | 10.5  |                              |                                |

**Notes:** <sup>a</sup>Adverse events were included only if reported in at least 10% of patients in one or more studies. <sup>b</sup>Total "n" represents sum of patients on all doses used in the study.

Overall, however, rates of withdrawal from trials of sertindole were low, ranging from 0.4% to 12.2% within the 6 trials included in Table 2. Limited naturalistic data also indicate that sertindole is well tolerated relative to other antipsychotic agents. In an observational study of 53 outpatients with psychotic illness who had switched from either a conventional or atypical neuroleptic to sertindole, clinicians rated the side-effect profile of sertindole as better (71%), comparable (18%), and worse (7%) than the previous medication.<sup>80</sup>

## Cognition

Cognitive dysfunction in schizophrenia remains one of the most devastating, functionally impairing aspects of the illness and as such has been an important target of antipsychotic drug development recently. The impact of second-generation antipsychotics on cognitive impairment is quite variable insofar as these agents have been found both to improve and to impair it further. One of the most well-studied paradigms to examine the effect of antipsychotic drugs on cognition is the water maze test, which depends on the function of working memory, learning, and attention. Two preclinical studies have demonstrated that sertindole, administered both acutely and as a 3-week pretreatment, did not impair performance in the water maze test, whereas both clozapine and olanzapine were noted to impair performance.<sup>99,100</sup> In another water maze task, sertindole was similarly found to reverse phencyclidine (PCP)-induced deficits in learning and memory 1 day earlier than clozapine or risperidone.<sup>101</sup> Sertindole furthermore reversed PCP-induced deficits in a measure of cognitive flexibility similar to modafinil<sup>102</sup> but unlike both haloperidol and second-generation agents, including clozapine, risperidone, and olanzapine.<sup>103</sup> Importantly, this PCP-induced deficit in cognitive flexibility was also reversed by a 5-HT<sub>6</sub> antagonist while a selective 5-HT<sub>2A</sub> receptor antagonist was without effect, highlighting a receptor profile factor that distinguishes sertindole from risperidone. Indeed, other reports from the preclinical literature have identified 5-HT<sub>6</sub> mechanisms as being a novel target for cognition impairments associated with schizophrenia and other neuropsychiatric disorders.<sup>104–107</sup> Limited data from preclinical reports, therefore, suggest that sertindole may improve cognitive deficits in schizophrenia. Moreover, this improvement may be related to its unique absence of antimuscarinic and histamine H1 antagonist activity or to its 5-HT<sub>6</sub> antagonist activity, illuminating new avenues for receptor targeting in antipsychotic development.

Recently, several clinical studies have explored the potential for sertindole to ameliorate cognitive deficits in

patients with schizophrenia. In a randomized, double-blind trial comparing the effects of sertindole with haloperidol on cognitive dysfunction in 34 patients with schizophrenia, sertindole improved both reaction time and attentional set-shifting significantly more than haloperidol (which notably worsened reaction time) at 4 and 12 weeks, respectively.<sup>108</sup> In a fludeoxyglucose (FDG) PET study examining prefrontal cortical (PFC) activation in patients with schizophrenia treated with sertindole, relative glucose metabolic rate of the dorsolateral PFC in sertindole-treated patients, compared with untreated patients and haloperidol-treated patients, was found to approach the metabolic rate of normal controls.<sup>109</sup> The ability of sertindole to improve cognitive impairment in schizophrenia may accordingly relate to its selectivity for cortical and limbic structures, where 5-HT<sub>6</sub> receptor antagonism has been associated with dopamine release and cognitive enhancement in preclinical models.<sup>105,110</sup>

## Suicide

Suicide remains one of the leading causes of death among patients with schizophrenia, affecting 9%–13% of this population.<sup>111</sup> Evidence that clozapine (vs olanzapine) may improve suicide rates has prompted further research into elucidating the differential impact of atypical antipsychotics on this phenomenon.<sup>112</sup> A subanalysis of the SCoP study following 4,905 patients treated with sertindole (12 mg/d) and 4,904 patients treated with risperidone (4 mg/d) for up to 63.5 months revealed a significantly lower incidence of suicide attempts ( $P = 0.037$ ; fatal plus nonfatal) among those treated with sertindole.<sup>113</sup> This difference in suicide rates was most pronounced during the first year of treatment, when more than 80% of the suicide attempts occurred ( $P = 0.0058$ ). Although there were fewer completed suicides among patients treated with sertindole than with risperidone (0.14 vs 0.26 per 100 patient years of exposure; PYE), the difference was not significant. Although limited to one study, these data suggest a decreased risk of suicide with sertindole vs risperidone among patients with schizophrenia, including those with previous attempts, and support future comparisons in this regard with other atypical antipsychotic drugs.

## Patient perspectives: quality of life

Schizophrenia is a devastating illness that compromises familial, social, and occupational aspects of patients' lives from an early age. Moreover, individual responses to treatment with antipsychotic medications are highly variable and may further detract from a patient's quality of life if



symptoms are not adequately treated or if side effects are intolerable. Insofar as nonadherence predicts negative treatment outcomes,<sup>114</sup> significant attention is paid to the effects of antipsychotic medications on quality of life and treatment adherence. In this regard, a retrospective study of sertindole use after discontinuing treatment with another antipsychotic agent due to either lack of efficacy or adverse events supports improved quality of life with sertindole treatment.<sup>115</sup> The patients were followed as they discontinued 2 antipsychotic agents (periods 1 and 3, the latter lasting 7.1 months) to undergo treatment with sertindole 2 times over (periods 2 and 4; 8.7 and 6.4 months in duration, respectively). The average number of hospitalizations arising from worsening symptoms decreased significantly upon first switching to sertindole (from 3.4 to 1 hospitalization), as did the number of self-harm attempts (from 22.8% to 3.5%). Notably, the number of patients engaged in a stable relationship increased significantly during both periods of sertindole treatment (from 38.6% to 54.4% and then from 45.6% to 57.1%), while the number of patients employed more than doubled after switching to sertindole for the first time (from 14.0% to 31.6%). These findings suggest that patients may experience improvement in symptoms, as well as in social and occupational functioning, with sertindole use after discontinuing another antipsychotic agent that was either ineffective or associated with intolerable side effects.

In a year-long, double-blind trial of sertindole (24 mg/d) vs haloperidol (10 mg/d), sertindole use was similarly associated with an improvement in quality of life from baseline as measured by the Heinrichs Quality of Life Scale (a semi-structured interview), whereas a slight decrease in quality of life was noted for patients treated with haloperidol.<sup>76</sup> In the same study, the time to psychotic decompensation and subsequent hospitalization due to patient nonadherence was significantly longer in the sertindole group than in the haloperidol group; to this effect, fewer sertindole-treated patients were hospitalized (2 vs 12) or withdrawn from the study prematurely secondary to nonadherence (2 vs 13) than those treated with haloperidol. A case series additionally describes improvements in emotional reactivity, initiative, and interest in 1 patient switching from risperidone (on which she had otherwise done well) and an improvement in positive and negative symptoms, weight loss, and increased compliance in another patient switching from olanzapine.<sup>116</sup> On the basis of these reports, sertindole may represent a potential therapeutic alternative to improve quality of life among patients with persistent side effects and/or suboptimal efficacy on an alternative antipsychotic agent.<sup>4</sup>

## Conclusions and place in therapy

With all evidence taken together, the role of sertindole in a treatment regimen for schizophrenia seems to be a study in contrasts. On the one hand, there are a number of areas where the treatment efficacy with sertindole is clear. First, those patients who are likely to benefit from sertindole include those who have poor control of existing positive and negative symptoms. Sertindole demonstrated efficacy advantages compared with risperidone<sup>29,115</sup> and haloperidol<sup>75</sup> and continued to show improvement in CGI-I scores over a 12-month period.<sup>81</sup> Second, sertindole seems to be generally well tolerated, with fewer problematic side effects related to sedation and weight gain. Moreover, sertindole is one of the few antipsychotics that demonstrates little or no sedation, daytime drowsiness, or increased sleep time.<sup>117</sup> Sertindole's lack of effect on muscarinic and histamine H1 receptors<sup>118</sup> undoubtedly contributes to the lack of sedation, but it is also important insofar as sertindole is not associated with anticholinergic-mediated cognitive impairment<sup>77</sup> or excessive weight gain.<sup>29,77,81</sup> Third, sertindole treatment regimens result in placebo-level EPS measures, which compares favorably with even the lowest doses of haloperidol (4 mg/d) examined,<sup>75</sup> thus reinforcing the notion that sertindole might prove valuable on more severe, late-occurring movement disorders.<sup>93</sup> Fourth, and perhaps most importantly, sertindole is one of the few atypical antipsychotics that has demonstrated a reliable and robust improvement in cognitive function in both preclinical<sup>102,103,119</sup> and clinical samples.<sup>35</sup> This is perhaps the factor that distinguishes it from most other atypical antipsychotics.

Another factor for consideration is that sertindole does display sexual side effects, producing decreased ejaculatory volume in more than 20% of men.<sup>35</sup> That said, other antipsychotics (eg, risperidone, thioridazine) have also been demonstrated to produce sexual side effects,<sup>97,98</sup> and the rate of sertindole discontinuation because of decreased ejaculatory volume was only 3%.<sup>35</sup> Thus, although this effect is notable given the incidence rate, it does not appear to represent a barrier to treatment, and it is unclear as to whether it constitutes a problematic side effect at a practical level.

Finally, there are 2 main considerations that may limit utilization of sertindole. First and foremost, sertindole is contraindicated for any patients with significant cardiovascular disease or existing QT prolongation issues. One of the key requirements for the reintroduction of sertindole to the European market was mandatory ECG monitoring both before and during treatment. Thus, in a fashion similar to monitoring clozapine patients for the development of

agranulocytosis, monitoring sertindole patients may represent an additional treatment burden and concern for both the patient and the treatment team. Moreover, these criteria likely disproportionately impact older patients, individuals with comorbid cardiovascular risk factors, and those taking multiple medications. Thus, the pool of patients most likely to benefit from sertindole may be smaller than for other atypical antipsychotics. Regardless, thorough screening and continued monitoring of sertindole patients are a necessity.

Second, there is a paucity of data comparing sertindole to a range of other atypical antipsychotics. Much of the literature to this point has drawn mostly favorable comparisons to haloperidol and risperidone, and although the superior efficacy vs haloperidol is not surprising, the favorable outcomes vs risperidone are very encouraging. However, robust comparison with other atypicals (eg, clozapine, olanzapine, quetiapine, aripiprazole) is warranted. Although preclinical and clinical data collected to date are encouraging (eg, sertindole appears to have a superior efficacy profile related to cognition, weight gain, and PANSS), it is only with more complete comparative effectiveness testing vs both placebo and multiple alternative atypical treatment regimens<sup>120</sup> that the true effectiveness of sertindole in therapy can be elucidated.

## Disclosure

The authors report no conflicts of interest in this work.

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