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REVIEW

Sertindole in the Management of Schizophrenia

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Abstract: Nowadays, new schizophrenia treatments are more ambitious than ever, aiming not only to improve psychotic symptoms, but also quality of life and social reinsertion. Our objective is to briefly but critically review the diagnosis of schizophrenia, the atypical antipsychotics sertindole's pharmacology, safety and status, and mainly evaluate the effects of sertindole compared with other second generation antipsychotics for people with schizophrenia and schizophrenia-like psychosis. In vitro studies showed that sertindole exerts a potent antagonism at serotonin 5-HT_{2A}, 5-HT_{2C}, dopamine D_2, and α_1 adrenergic receptors. Sertindole offers an alternative treatment option for refractory patients given its good EPS profile, favorable metabolic profile, and comparable efficacy to risperidone. Due to cardiovascular safety concerns, sertindole is available as a second-line choice for patients intolerant to other antipsychotic agents. Further clinical studies, mainly comparisons with other second-generation antipsychotic agents, are needed to define the role of sertindole in the treatment of schizophrenia.

Keywords: sertindole, antipsychotics, pharmacology, pharmacokinetics, efficacy, safety

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Introduction

Nowadays, new treatments for schizophrenia are more ambitious, aiming to improve not only psychotic symptoms, but also quality of life and social reinsertion. For many years, it was widely accepted that any effective drugs for schizophrenia would also induce extrapyramidal side effects (EPS), and the term "neuroleptic" was originally used to describe such neurologic side effects.[1] 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.[2] However, negative symptoms are probably the more disabling, and patients may not respond as well to typical antipsychotic drugs. In addition to efficacy issues, safety of medication also influences the choice of antipsychotic agent.[3]

Sertindole is an atypical antipsychotic, which is thought to give a lower incidence of extrapyramidal side effects at clinically effective doses than typical antipsychotic drugs. Sertindole is a second-generation antipsychotic recently reintroduced in the market for the treatment of schizophrenia after a reevaluation of its risks and benefits.[4] Our aim in this review is to provide an overview of the pharmacological properties of sertindole as well as of its efficacy, tolerability and safety profile. Moreover, to determine the effects of sertindole compared with placebo, typical and other atypical antipsychotic drugs for schizophrenia and related psychoses.

Diagnosis of Schizophrenia

Schizophrenia is a chronic, complex, and heterogeneous disease that affects most aspects of psychological functioning. It can have a devastating impact on familial, social and vocational aspects of patients' lives.[4] Long-term treatment with antipsychotic drugs is the major factor in preventing relapse. Up until the early 1980s, schizophrenia diagnoses remained debatable.[5] The lack of uniform diagnostic criteria led to variations in the relative rates of schizophrenia by population. For example, in New York and London, as demonstrated in an important study which became known as the United States–United Kingdom Study.[6]

A recent study using standardized criteria[5] showed similar prevalence of schizophrenia and mood disorders across the Atlantic.[2] The DSM-III (Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition)[7] incorporated criteria developed by Feighner et al[8]—the Washington University Criteria, which required the presence of symptoms for at least 6 months.

Such criteria established schizophrenia as a chronic and severe disorder, with few patients achieving full recovery.[2] Currently, the DSM is in its 4th version[9] and its diagnostic criteria are used-worldwide, standardizing the diagnosis of schizophrenia and allowing results of clinical trials to be compared, see Table 1. Advances in two other fields have led to great improvement in our understanding and diagnosis of schizophrenia: neuroimaging studies and genetics. In 1980, Crow[10] made a distinction between schizophrenia type I, with more positive symptoms correlated with increased dopamine (DA) type 2 receptors and type II schizophrenia, with more negative symptoms correlated with an enlarged ventricle and a diminished cerebral cortex. Positive symptoms include unusual experiences such as perceptual abnormalities (hallucinations) and fixed, false, irrational beliefs (delusions). Negative symptoms comprise a lack of ordinary mental activities such as thoughts and motivation.[10]

The disease is frequently associated with cognitive and depressive symptoms and commonly manifests at an early adult age. Studies using magnetic resonance imaging (MRI) have demonstrated structural and functional brain abnormalities, predominantly involving frontal and temporal lobes, and in most cases already present at the onset of illness, which usually manifests during adolescence or young adulthood.[1,2]

Atypical Antipsychotics

Atypical antipsychotic drugs, by definition, differ from typical antipsychotic agents in producing significantly fewer EPS and carrying a lower risk of TD in vulnerable clinical populations at doses that result in comparable control of psychosis.[11–14] The term atypical has been used too promiscuously for it to have a robust scientific meaning. Yet, there markable frequency of its use, coupled with the failure of more scientifically reliable terms to replace it, suggests that the term conveys a valuable meaning. It was first

Table 1. Diagnostic criteria for schizophrenia—DSM-IV-TR criteria.[9]

A. *Characteristic symptoms*: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):
   1. Delusions
   2. Hallucinations
   3. Disorganized speech (eg, frequent derailment or incoherence)
   4. Grossly disorganized or catatonic behavior
   5. Negative symptoms, ie, affective flattening, alogia, or avolition.

B. *Social/occupational dysfunction*: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. *Duration*: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (ie, active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (eg, odd beliefs, unusual perceptual experiences).

D. *Schizoaffective and mood disorder exclusion*: Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either 1) no Major Depressive, Manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or 2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. *Substance/general medical condition exclusion*: The disturbance is not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition.

F. *relationship to a pervasive developmental disorder*: If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Classification of longitudinal course (can be applied only after at least 1 year has elapsed since the initial onset of active-phase symptoms).

introduced to describe clozapine, since its properties were found to be different from the older, conventional, or typical neuroleptics.[15] 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 TD or dystonia after being administered chronically.[16,17]

At least in clinical circles most would agree that clozapine, risperidone, olanzapine, quetiapine, sertindole, ziprasidone and now sertindole, aripiprazole and amisulpride are atypical—even though many of those agreeing to the above list may disagree on their criteria of definition.[18,19]

When compared with older antipsychotic drugs, atypical antipsychotics show fewer EPS and require less concomitant anticholinergic use, evenwhen controlling for high doses of haloperidol that have been conventionally used in such studies.[20] The second most commonly shared feature is that most of the newer atypical antipsychotics show either no, or only transient, prolactin (PRL) 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 DA blockade in the pituitary that lies outside the blood–brain barrier.[21] '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.[22] The atypical antipsychotic drugs are also thought to be more effective than conventional drugs in the treatment of negative symptoms in schizophrenia, although this has not yet been adequately established.[23] At present, new antipsychotics are routinely investigated for their possible effect on negative symptoms. In spite of their better tolerability profile, the clinical antipsychotic trials of intervention effectiveness (CATIE)[24] showed a high drop outrate with atypical antipsychotics because of either inefficacy or intolerable side-effects. Nevertheless, the safety advantages of the atypical drugs have been questioned, as their use is associated with differential risk of metabolic

effect, such as weight gain, lipid dysregulation and hyperglycemia,[8] and cardiovascular adverse events, particularly prolongation of heart-rate corrected QT interval (QTc) of the electrocardiogram (ECG).[25,26]

Sertindole

Sertindole is an atypical antipsychotic drug indicated for the treatment of schizophrenia. It was first authorised in the United Kingdom in 1996 and subsequently in other European countries.[27]

Preclinical data[28] and premarketing clinical trials[29,30] had shown the drug's capacity to prolong the QT interval, but without apparently increasing the risk of cardiac death and authorities did not require any strong warning or electrocardiographic (ECG) surveillance upon first licensing. Upon extension of the drug license to other European markets in 1997, authorities asked for a change in the Summary of Product Characteristics (SPC) that would include ECG surveillance prior to and during the treatment with sertindole. A drug alert regarding sertindole originated subsequently from the UK MCA's database of spontaneous reports, Adverse Drug Reaction Online Information Tracking (ADROIT), in early 1998.[31]

The proportion of reports of sudden or unexpected deaths to total reports was about ten times higher for sertindole (7.5%) than for the other atypical antipsychotics olanzapine (0.8%) and risperidone (0.8%).[32,33] By the end of November 1998, the Committee on Safety of Medicines (CSM), and the Medicine Control Agency (MCA) had been notified of 36 suspected adverse drug reactions with a fatal outcome and 13 reports of serious, nonfatal arrythmias in patients treated with sertindole. This potential effect, ascribed to the QT-interval prolongation induced by sertindole, led to the suspension of all European Union marketing authorizations in 1998, pending a full evaluation of its risk-benefit profile.[33] Since then, nonclinical data showed that QT-interval prolongation was not related with ventricular arrhythmias. Moreover, results from epidemiological studies failed to confirm the ADROIT signal and did not indicate an excess of overall mortality with sertindole relative to other recently developed antipsychotics.[34]

Based on this evidence, the Committee for Medicinal Products for Human Use (CHMP) opted to reintroduce sertindole for use in Europe under certain restrictions, such as on a named-patient/compassionate use program (NPU) inpost-marketing surveillance studies. Sertindole was finally approved by the European Commission and made available in the European market in 2006.[35]

Pharmacology

Sertindole is a phenylindole derivative (1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl-2-imidazolidinone). In vitro studies showed that sertindole exerts a potent antagonism at serotonin 5-HT_{2A}, 5-HT_{2C}, dopamine D_2, and α_1-adrenergic receptors, with binding affinities of 0.20, 0.51, 0.45, and 1.4 nmol, respectively, whereas it has a low affinity for cholinergic muscarinic, histamine H1, and α_1-adrenergic receptors.[36] The effect on D_2 receptors is more pronounced in the limbic dopamine system compared with the nigrostriatal system. This is supported by findings from clinical trials that provide evidence for significantly fewer extra pyramidal side effects than haloperidol and risperidone.[37] However, sertindole seems to bind rather firmly to the receptors since extra washing procedures did not diminish the specific binding of ligand to 5-HT_2 receptors, D_2 receptors or α-$_1$adreno receptors. The results indicate that sertindole readily passes the blood-brain barrier and remains at central monaminergic receptors for quite a long time. Twenty-four hours after a single dose of sertindole the compound binds to 5-HT_2 receptors, α_1-adrenoceptors and D_2 receptors was found in a dose-dependent.[37]

In line with behavioural experiments[38] sertindole in these ex vivo experiments has the highest effect on 5-HT_2 receptors, a lower effect on α_1-adrenoreceptors and the lowest effect on DAD_2 receptors. The effect is lower in striatum than in limbic tissue. However, the difference in effect on DA receptors in the two regions in no way resembles the large difference in effect on limbic DA neurones in VTA versus striatal neurones in SNC.[39]

Although sertindole in vivo has high and equal affinity for D_2 and 5-HT_2 receptors it shows considerably lower activity in the ex vivo experiments on D_2 receptors than on 5-HT_2 receptors.[39] No explantation for this discrepancy can be given although one may speculate that the rate of dissociation from D_2 receptors is faster than from 5-HT_2 receptors. Another explantation could be that sertindole is metabolized

to compounds which have higher affinty for 5-HT_2 receptors but have much lower affinity for D_2 receptors than sertindole.[38] This difficulty is also apparent when discussing the appearance of blockade of DA neurones in VTA (and SNC) after 3 weeks of treatment, since no increase infiring rate is seen after acute treatment with sertindole.[37–40]

In contrast to other antipsychotics, sertindole is not associated with sedative effects; sedation may add to the cognitive problems inherent in schizophrenia. Further to that, studies show that sertindole effectively normalizes laboratory induced cognitive impairment in animals, and that sertindole treatment has shown long lasting improvements in elementary cognitive processes in humans.[38,39] This advantage may be linked to the high $5HT_{6a}$ receptor affinity. In conclusion sertindole is a potent, long acting compound which readily passes the blood-brain barrier. It dose-dependently binds to all three receptors types. In line with in vivo behavioural experiments sertindole has the most pronounced effect on 5-HT_2 receptors, lower effect on α_1-adrenoceptors and the lowest effect on striatal D_2 receptors on dopamine neurones in the rat.[39]

Sertindole is slowly absorbed by the gastrointestinal tract, reaching peak concentrations within ten hours after oral doses in healthy subjects and renally impaired patients. The relative bioavailability of the tablet formulation is about 75% and absorption is significantly affected by food or antacids.[41–43]

Over the dose range of 4–16 mg/day, dose-proportional increases in the maximum plasma concentrations (C_{max}) [from 2.0 to 9.1 ng/mL] and the area under the plasmaconcentration-time curve (AUC from 170 to 572 ng·h/mL) of sertindole have been documented.[44]

Sertindole undergoes extensive metabolism in the liver by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4, to two main metabolites, dehydrosertindole (via oxidation) and norsertindole (via N-dealkylation) with negligible effects in humans. Genetic polymorphism of the CYP2D6 isoform leads to a moderate inter individual variation in the pharmacokinetics of sertindole, with reduction in sertindole clearance up to 67% and plasma sertindole concentrations 2–3 times higher in poor metabolizers (PM, up to 10% of the general population) when compared with extensive metabolizers (EM). Sertindole and its metabolites are excreted slowly, mainly in the feces with a minor amount appearing in the urine. Its mean terminal half-life is 53–102 hours, as evidenced in single- and multiple-dose studies in healthy subjects; therefore, steady-state is reached within 2–3 weeks.[41,42]

The relatively long half-life of sertindole in comparison to other atypical antipsychotics may represent a potential benefit in clinical practice and patient compliance. Neither gender nor age seem to affect the pharmacokinetics of sertindole. Concomitant treatment with fluoxetine, paroxetine and quinidine (CYP2D6 inhibitors) and erythromycin, ketoconazole and indinavir (CYP3A4 inhibitors), may raise plasma sertindole concentrations. Nevertheless, oral coadministration of erythromycin, 250 mg 4 times/day, caused a slight increase in plasma AUC of sertindole given as a single 4 mg dose to healthy subjects.[45]

On the other hand, plasma sertindole concentrations may decrease during concomitant treatment with CYP inducers such as carbamazepine, rifampicin, phenobarbital, and phenytoin. Because of the effect on QTc interval, sertindole is contraindicated in combination with drugs known to significantly increase the QTc interval, such as some antihistamines (terfenadine and astemizole), some antiarrhythmics (amiodarone and quinidine), quinolone antibiotics, and many antipsychotics and antidepressants.[46]

Sertindole in Schizophrenia

Several clinical trials and large-scale epidemiological studies have evaluated the efficacy and tolerability of sertindole in patients with schizophrenia. But the efficacy of sertindole in patients with schizophrenia has been established in five randomized, double-blind clinical trials, without considering results from smaller studies presented as case reports, posters, and proceedings of congresses.[47] These studies included a randomized, controlled, dose-ranging trial, involving 205 participants, evaluated the efficacy of sertindole, administered at the dosage of 8–20 mg/day for 6–7 weeks, in the treatment of schizophrenia. Sertindole at the dose of 20 mg/day was more effective than placebo in reducing Positive and Negative Syndrome Scale (PANSS), and brief Psychiatric Rating Scale (BPRS) total scores. At the end of the trial, significantly more patients treated with sertindole (20 mg/day) than with placebo were "very

much improved" (20% vs. 3%; $P < 0.05$) considering Clinical Global Impression (CGI) scores.[48] In a multicenter, double-blind, placebo-controlled study,[49] 497 hospitalized patients with schizophrenia and active psychosis were randomized to receive sertindole 12, 20 or 24 mg/day, haloperidol 4, 8 or 16 mg/day, or placebo for an 8-week period. Measures of efficacy included PANSS, the Scale for the Assessment of Negative Symptoms (SANS), the CGI scale, and the BPRS. Both sertindole and haloperidol were significantly more effective than placebo in the treatment of psychosis, as documented by improvements from baseline in PANSS and BPRS total scores at the end of the trial. Sertindole and haloperidol were equally effective, with the best results seen with the 20 mg/day dose of sertindole and the 8 mg/day dose of haloperidol.

Another multicenter, double-blind study,[50] involved 617 patients who were randomized to receive sertindole (8, 16, 20 or 24 mg/day) or haloperidol (10 mg/day) for 8 weeks. A significant reduction in PANSS total-score was observed with sertindole (16 mg/day) and with haloperidol (10 mg/day) compared to recipients of the sub-therapeutic 8 mg/day dose of sertindole. In this study, sertindole (16 mg/day) was at least as effective as the two higher doses. The results of these two comparative trials with haloperidol have suggested that sertindole was more effective against negative symptoms; moreover, sertindole (16 mg/day) was as efficacious as (20 mg/day), suggesting that the initial titration should be made to (16 mg/day). Additional evidence provided from the overmentioned studies is that sertindole (24 mg/day) did not appear to be any more efficacious than 20 mg/day, the recommended-prescribed dose range is (16–20 mg/day).[50]

The longer term efficacy of sertindole was assessed in a double-blind, 12-month trial comparing (24 mg/day) sertindole with (10 mg/day) haloperidol in 282 outpatients with schizophrenia.[51] At one year, a greater number of participants who were treated with haloperidol as compared to sertindole (24 mg/day) were leaving the study early due to any reason or non-compliance). However, at six weeks, there was no statistically significant difference between sertindole (at 8, 16, 20, or 24 mg) and haloperidol for this latter outcome. The incidence of EPS was higher among those treated with haloperidol than sertindole at (8, 16, 20 or 24 mg/day). More participants treated with haloperidol experienced akathisia, tremor and hypertonia than those treated with sertindole. At one year, 33 participants treated with sertindole (24 mg) had experienced the sexual adverse event of decreased ejaculatory volume, compared with six participants treated with haloperidol.[51] However the number of included male participants was not reported and therefore the RR could not be calculated. At one year, more participants taking sertindole (24 mg/day) had put on weight compared to those taking. At six weeks, all of the sertindole groups showed an increase in body weight from baseline to final evaluation ranging from 1.3 kg to 1.9 kg, all of which represented a statistically significantly different weight change than that recorded for the haloperidol treatment group.[51]

A double-blind, parallel-group, flexible-dose, multicenter study compared the efficacy and tolerability of sertindole (12–24 mg/day; n = 98) with risperidone (4–10 mg/day; n = 89) in 187 out- and inpatients with various subtypes of schizophrenia who had to be at least moderately ill.[52] The study terminated prematurely because of the temporary withdrawal of sertindole from the European Union market. After 12 weeks of treatment, improvements in positive and negative symptoms were seen in both treatment groups. Sertindole treated patients had a greater reduction in PANSS negative subscale scores. However, data for leaving the study early were available but the total was high (35.8%).[52]

Leucht et al[53] 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, extrapyramidal side-effects, 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. With regard to quality of life, only clozapine, sertindole and amisulpride were better than first-generation drugs.[53]

Sertindole versus placebo:[54] Sertindole (at 20 mg/day) was found to be more effective than

placebo in terms of BPRS total scores and CGI total end point scores. A marginally statistically significantly greater number of participants that were treated with 20 mg of sertindole were reported to have been 'very much improved' as compared to those taking placebo. There was no statistically significant difference between sertindole (at 8 or 12 mg/day) and placebo for these three outcome measures. There were no statistically significant differences between sertindole (8, 12 or 20 mg) and placebo for the incidence of extrapyramidal symptoms, extrapyramidal related events or use of medication to avoid extrapyramidal symptoms. There were no statistically significant differences found between sertindole and placebo for the movement disorders akathisia, hypertonia and tremor or somnolence. At eight weeks a statistically significant difference between placebo and all sertindole groups (8, 12 and 20 mg) for mean change from baseline in the QT and QTc intervals were observed. There was a statistically significant greater mean weight gain among participants taking sertindole (20 mg, mean weight gain of 3.3 kg) as compared to placebo (mean weight gain of 0.8 kg; $P < 0.05$).[54]

In a multicenter, phase 3, randomized, double-blind, parallel-group study, only patients with DSM-IV schizophrenia who had failed an adequate antipsychotic treatment within the previous 6 months and who had not responded positively to haloperidol during screening were included.[55] The primary efficacy variable was change in PANSS from baseline to final assessment. Weekly assessments included the PANSS, the BPRS, the SANS, and the CGI scale. Of the 321 patients randomly assigned to double-blind treatment, 217 patients completed the study (sertindole, n/n = 142/216 [66%]; risperidone, n/n = 75/105 [71%]). There were no statistically significant differences between the groups in any of the secondary end points: PANSS positive and negative subscales, CGI scores, BPRS total scores and positive symptom subscale scores, and SANS total scores. Patients reported similar levels of adverse events and treatment-emergent adverse events (TEAEs), except for extrapyramidal syndrome-related, which were more common in the risperidone-treated group.[55] Prolongation of the QTc interval was observed significantly more frequently with sertindole treatment. The data suggested that Sertindole and risperidone are effective and well-tolerated in patients with treatment-resistant schizophrenia. Sertindole offers an alternative treatment option for refractory patients given its good EPS profile, favorable metabolic profile, and comparable efficacy to risperidone.[55]

Moreover, data are limited on the effectiveness of sertindole in the maintenance treatment of schizophrenia.

Safety and Status

Experience with sertindole in acute overdose is limited; the drug appears to be relatively safe in overdose on its own, as patients taking estimated dosages up to 840 mg have recovered without sequelae. Reported signs and symptoms of overdose were dyspnea, somnolence, slurred speech, tachycardia, hypotension, transient AV-block and QT-c prolongation; cases of Torsades de Pointes (TdP) have been observed, often when sertindole was combined with other drugs known to induce TdP. In overdose cases, due to the long half-life of sertindole in humans (3–5 day), and its QT prolongation capacity, therapeutic drug monitoring would be useful to follow the sertindole concentrations.[57] In clinical practice, its corrected form for heart rate (QTc) is used, since the QT interval shortens with increasing heart rates. Prolonged QTc interval increases the risk of cardiac arrhythmias and may predispose to the development of ventricular tachyarrhythmias QTc intervals are usually around 400 msec in duration, and values below 440 are considered normal. The greater the duration, the more likely torsade de pointes becomes, but 500 msec has frequently been used as a cut-off because longer QTc interval measures are associated with substantially higher risk. Sertindole showed a dose-dependent increase in the QTc interval that averaged 22 msec at usual therapeutic doses, whereas a QTc interval, 500 msec was observed in approximately 2% of 2194 sertindole-treated patients.[59,60]

In a long-term study,[51] only one participant from the sertindole group (24 mg) had a QT interval that exceeded 500 msec. However, 11 sertindole treated participants had QTc intervals of at least 500 msec, compared to none in the haloperidol treated group (8% vs. 0%, $P < 0.05$). In the risperidone-controlled trial by Azorin et al,[52] significantly more sertindole-treated patients reported QT prolongation (22.7% versus 4.5%); moreover, of the 12 (12%) premature dropouts during sertindole treatment, six

were due to QTc interval prolongation. Beyond sertindole, many conventional and atypical antipsychotics have been related to prolongation of QTc.[61] The most compelling evidence exists with thioridazine which has been reported to increase QTc about of 30 msec, followed by ziprasidone (15.9 msec), haloperidol (7.1 msec), quetiapine (5.7 msec), risperidone (3.6–3.9 msec), and olanzapine (1.7 msec).[62]

Generally, drug-induced arrhythmias are more likely to occur in patients with pre-existing QT prolongation, which may be congenital or due to many causes (myocardial disease, left ventricular hypertrophy, malnourishment, alcoholism, ischemia, or potassium depletion). Moreover, drug interactions must be taken into account, as drugs with minimal QTc interval prolongation may interact with other compounds, competing for the same metabolic way.[61,62]

Results from a safety database of approximately 2500 patients treated with sertindole in clinical trials evidenced that 89% of patients reported at least one treatment-emergent adverse event. The most commonly reported adverse events associated with sertindole treatment were headhache (33.8% of patients), insomnia (31.3%), rhinitis/nasal congestion (28.5%), and, in male patients, decreased ejaculatory volume (21.8%). Sertindole is not associated with sedation; with regard to anticholinergic effects, dry mouth and constipation occurred in 10% of patients.[65]

The mechanism of a reduction in ejaculation volume during treatment with sertindole, a side-effect usually not associated with erectile disturbances or decreases in libido, is as yet not precisely known; this effect might be due to the α_1-noradrenergic antagonistic properties of sertindole, and it probably does not involve retrograde ejaculation as no semen could be detected in the urine after orgasm.[48] An alternative mechanism has been suggested involving calcium channels on the vas deferens as, in vitro, contractions of the vas deferens are known to be affected by calcium channel antagonists. Sertindole, such as other antipsychotics, has the property to block sodium and calcium influx channels, so this may contribute to decreased ejaculatory volume.[50]

In addition to EPS, important AEs associated with atypical antipsychotics are the drugs' prolactin profile, weight gain, and alteration of glucose and lipid metabolism. Sertindole does not cause clinically significant increases in prolactin, in short- or long-term clinical studies.[50,51] Similarly to other atypical antipsychotics, sertindole appears to induce a moderate weight gain, presumably related to the high affinity for 5-HT_{2C} receptors. In the placebo-controlled clinical trials, there was a statistically significant greater mean weight gain among participants taking sertindole (20 mg, mean weight gain of 3.3 kg) as compared to placebo (mean weight gain of 0.8 kg; $P < 0.05$).[58]

Minor increases in plasma levels of glucose, cholesterol and triglycerides have been reported in short-term studies;[56] increased mean plasma cholesterol levels in one trial ($P < 0.05$ vs. placebo) were documented.[50]

The improvements in all criteria during the sertindole treatment periods provide evidence of a subgroup of patients who respond particularly well to this drug. In particular, the reduction in number of hospitalizations due to worsening of psychotic symptoms provides objective evidence for this improvement, as hospitalization for worsening of psychosis has been demonstrated to be a good indicator of relapse in patients with schizophrenia.[63]

Why a particular subgroup of patients responds to sertindole in this way is unknown, but it may be related to the specific chemical structure and the specific receptor profile which lead to the unique pharmacological profile of the drug.[64] This is characterised by selective inhibition of dopaminergic activity in the mesolimbic pathway, with very little inhibition of the nigrostriatal dopaminergic neurons.[65]

Findings from controlled clinical trials have demonstrated that sertindole is at least as effective as haloperidol and risperidone against the positive symptoms of schizophrenia, while it appears superior against negative symptoms. Preliminary evidence suggests that sertindole has beneficial effects on cognitive function. Sertindole is associated with a low rate of extrapyramidal side effects, lacks sedative properties, and may induce a moderate weight gain. No clinically relevant elevations in serum prolactin, glucose or lipid levels have been so far documented in sertindole-treated patients. On the other hand, administration of sertindole may result in a prolongation of the QTc interval, with subsequent risk of serious arrhythmias. However, postmarketing surveillance studies have recently indicated that sertindole is not associated with a higher rate of cardiovascular mortality than other antipsychotic agents.[46,60–63]

Conclusions

The potential for cardiac adverse events associated with sertindole is balanced by a tolerability profile characterized by the low liability to induce sedation, hyperprolactinemia, and EPS. With regard to tardive dyskinesia, there are no available data. Preliminary evidence suggests that sertindole is not associated with a increased risk of diabetes; however, its effect on serum glucose and lipid levels need further investigation. Beyond the risk of synergistic effects with other drugs inducing QTc prolongation, whose use is contraindicated, the metabolic drug interaction profile of sertindole is far from being elucidated. Sertindole at a dose of 20 mg/day was found to be more antipsychotic than placebo. When used at 8, 12 or 20 mg/day it appears to be as acceptable as placebo (in terms of various adverse events including movement disorders and somnolence), but seems to be associated with more cardiac problems (8, 12 or 20 mg/day) and an increase in weight gain (20 mg/day) than placebo. Sertindole at a dose of 24 mg/day was better tolerated than haloperidol (in terms of participants leaving the study early). It was also found to be was associated with fewer movement disorders (at 8, 16, 20 or 24 mg/day) and sedation (8 or 24 mg/day) than haloperidol. However, it was shown to cause more cardiac anomalies (16, 20 or 24 mg/day), weight gain (all doses combined), rhinitis (16 or 24 mg/day), and problems with sexual functioning (24 mg/day) than haloperidol. One short term study reported that sertindole 16 mg/day was the most optimal dose. Except for risperidone, no randomized trials have compared sertindole with other second-generation antipsychotic drugs. Further "head-to-head" comparisons with other second-generation antipsychotic drugs are strongly needed. Information on the efficacy and safety of sertindole in special populations such as children and adolescents, elderly patients, and subjects with treatment-refractory schizophrenia is still limited or lacking.

At the present, it is difficult to define the place of sertindole in the management of schizophrenia in the next few years. The prolonged marketing suspension of sertindole involved considerable medical and administrative restrictionson its supply and use, and had a significant impact on research. As a consequence, available data on its efficacy, safety, and tolerability profile are still sparse and incomplete. Therefore, considering its nonsedating properties, sertindole should not be used in emergency situations for urgent relief of symptoms in acutely disturbed patients. Further independent and appropriately clinical studies, direct comparisons with other second-generation antipsychotic agents, are needed to clinically define the role of sertindole in the treatment of schizophrenia.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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