Introduction

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Dopamine (D_2) receptor antagonists have formed the mainstay of treatment for psychotic disorders for more than four decades. Therapy has traditionally been limited to phenothiazine and butyrophenone derivatives such as chlorpromazine and haloperidol, the actions of which are thought to be mediated by blockade of D_2 receptors [1, 2]. Although these conventional antipsychotic agents usually improve the positive symptoms of schizophrenia and help to prevent relapse, they have only a marginal effect on negative symptoms [3], cognitive impairment [4], and mood disturbances [5, 6], all of which are common in patients with schizophrenia. Moreover, these agents are typically associated with a high incidence of extrapyramidal symptoms, parkinsonism, tardive dyskinesia [7], and other side-effects.

Clozapine, which is structurally distinct from conventional antipsychotics, was the first member of a novel group of antipsychotic agents to improve psychotic symptoms with minimal risk of extrapyramidal symptoms [8]. However, its clinical usefulness is limited by its potential to cause agranulocytosis in approximately 1% of patients, which has largely restricted its use to the treatment of treatment-resistant schizophrenia.

The clinical effectiveness of clozapine is postulated to be related to relatively weak D_2 receptor affinity and potent serotonin $(5\text{-HT})_{2A}$ receptor antagonism. This has, in part, led to the hypothesis that antagonism of serotonin receptors in the brain and a high $5\text{-HT}_{2A}/D_2$ binding affinity ratio limits the emergence of extrapyramidal symptoms, and, at the same time, improves efficacy in negative symptoms of schizophrenia [8, 9].

Since the discovery of clozapine, several novel antipsychotic agents have been developed. The potential benefits that these novel agents may offer include: broader spectrum of symptom improvement, fewer or no extrapyramidal symptoms, minimal risk of tardive dyskinesia, and reduction or absence of prolactin elevation and related side-effects. Although the novel antipsychotics share certain features, their pharmacology is diverse, predicting functional differences, many of which have been observed in clinical trials. Thus, there are notable differences in the side-effect profiles of the various atypical antipsychotics [10–13], and some differences are beginning to develop in the efficacy profiles for these agents.

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Ziprasidone is a novel antipsychotic in late-stage clinical development. It is chemically distinct from clozapine and has a unique receptor profile that distinguishes it from other antipsychotic agents. Both *in vitro* and *in vivo* studies indicate that the affinity of ziprasidone for 5-HT_{2A} receptors is an order of magnitude greater than its affinity for D_2 receptors [14]. Ziprasidone also acts as a potent 5-HT_{1A} receptor agonist, is a potent 5-HT_{1D} and 5-HT_{2C} receptor antagonist, and moderately inhibits 5-HT and noradrenaline (NA) reuptake sites, actions which are thought to predict efficacy in reducing positive and negative symptoms of schizophrenia and associated symptoms of depression and anxiety, as well as having a low liability for inducing movement disorders [5, 15–18]. In addition, ziprasidone has negligible cholinergic (m_1) activity and only modest affinities for histaminic (H_1) and α_1-adrenoceptors, which predict low liability for cognitive impairment, sedation, and anticholinergic and cardiovascular side-effects [11, 12]. The pharmacology of ziprasidone also suggests a low propensity for some of the nonmotor side-effects of certain newer antipsychotics. Ziprasidone is a relatively less potent human α_1-adrenoceptor antagonist (relative to D_2) than several of the other novel antipsychotics, suggesting that it may be less likely to cause orthostatic hypotension. The 5-HT and NA reuptake inhibition, the potent 5-HT_{1A} agonist activity and the reduced H_1 and α_1 affinity compared with other antipsychotics may also offset the appetite stimulation and weight gain linked to 5-HT_{2C} receptor antagonist activity, and are believed to contribute to the low potential for weight gain associated with ziprasidone compared with other novel antipsychotics [19, 20].

An extensive clinical trials program has investigated the short-term use of oral ziprasidone in acutely ill patients with schizophrenia or schizoaffective disorder, and long-term use in stable patients with chronic or subchronic schizophrenia (the Ziprasidone Extended Use in Schizophrenia [ZEUS] trial). These studies have confirmed the therapeutic and tolerability advantages of ziprasidone over conventional antipsychotics. In the ZEUS study, ziprasidone treatment resulted in a lower probability of acute exacerbation over a 1-year period with continuing improvements in overall psychopathology and negative symptoms, compared with placebo [21]. Global function also improved over this time period. In several aspects, ziprasidone may offer efficacy and tolerability advantages over other novel antipsychotics as well.

The pharmacokinetics of ziprasidone have been characterized in both healthy volunteers and patients with schizophrenia. The papers presented in this supplement describe the pharmacokinetic and drug interaction profiles of ziprasidone. Studies have shown that ziprasidone exhibits linear and predictable pharmacokinetics and has a low potential for drug interactions. Administration with food increases the absorption of ziprasidone up to 100%, and when taken with food, the average absolute bioavailability is approximately 60% [22]. Ziprasidone is highly protein-bound (>99%). Ziprasidone is metabolized extensively with less than 1% of an oral dose excreted unchanged in urine and faeces. Human liver microsomes, probe substrates, and recombinant enzyme studies show CYP3A4 to be the primary isozyme responsible for the metabolism of ziprasidone [23]. The major metabolites formed are ziprasidone-sulfoxide and ziprasidone-sulphone. Both metabolites are clinically inactive. With multiple dosing, peak serum ziprasidone levels are observed at 6–8 h postdose. The mean half-life is about 7 h, suggesting that twice-daily dosing is appropriate, and steady-state plasma concentrations of ziprasidone are attained within 1–3 days of the initiation of oral therapy. At steady-state, systemic exposure is dose-proportional over the 20–80 mg twice-daily dose range. Age, gender, and mild or moderate renal or hepatic impairment have no clinically significant influence on ziprasidone exposure. Thus, dose adjustment may not be needed in the elderly or in those with mild or moderate renal or hepatic impairment.

Ziprasidone has little potential for interaction with drugs metabolized by cytochrome P450, or to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Co-administration of ziprasidone with other CYP3A4 substrate inhibitors or inducers does not appear to be problematic. In addition, no clinically significant interactions have been reported with lithium, combined oral contraceptives, or combined aluminium and magnesium hydroxide antacid.

In summary, ziprasidone is a novel antipsychotic with a unique array of pharmacological activities that predict a broad range of beneficial effects, as well as a low liability for inducing movement disorders, cardiovascular side-effects, sedation, and cognitive impairment. Ziprasidone exhibits linear and predictable pharmacokinetics and has a low potential for drug interactions. Overall, ziprasidone appears to offer important therapeutic and tolerability advantages over conventional, and some novel, antipsychotics.

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