with the reported ability of α_1 antagonists to suppress raphe neuronal activity. Desipramine did not reverse the inhibitory effect of ziprasidone. Oral (PO) 3.2 mg/kg ziprasidone and clozapine had no effect on dopamine release in the striatum (STR) of awake rats, but increased dopamine release in the prefrontal cortex (PFC) to 160%–180% of basal levels. Ziprasidone enhanced STR dopamine release after doses of ≥10 mg/kg PO, but still preferentially increased PFC dopamine release. Olanzapine produced similar increases in PFC and STR dopamine release. Pre-treatment with WAY-100635 (0.1 mg/kg subcutaneous; SC) inhibited the PFC dopamine release induced by 10 mg/kg PO ziprasidone by 80% and that induced by 3 mg/kg SC clozapine by 60%, but had no effect on olanzapine-induced PFC dopamine release. These results show that ziprasidone and clozapine, unlike olanzapine, act as $5HT_{1A}$ agonists *in vivo*. $5HT_{1A}$ agonist effects may contribute to the beneficial clinical effects seen in patients and could offer advantages over agents for the treatment of schizophrenia that do no activate $5HT_{1A}$ receptors.

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INTRAMUSCULAR (IM) ZIPRASIDONE VS. IM HALOPERIDOL IN PATIENTS WITH ACUTE, NON-ORGANIC PSYCHOSIS

S. Brook[1]*, M. Krams[2], K. Gunn[2]. [1]*Research Unit, Sterkfontain Hospital, Krugersdorp 1740, South Africa*
[2]*Central Research Division, Pfizer Inc, Sandwich, CT13 9NJ, UK*

This 7-day, randomized, open-label study compared the efficacy and tolerability of the rapid-acting intramuscular (IM) formulation of the novel antipsychotic, ziprasidone (n = 90), with IM haloperidol (n = 42) in the treatment of inpatients with acute, non-organic psychosis. Patients received up to 3 days of IM treatment followed by oral therapy until the end of the study. Doses, flexibly adjusted according to clinical need, were as follows: ziprasidone 10 mg IM on entry, followed by 5–20 mg IM 4–6 hourly (maximum daily dose, 80 mg); then by oral ziprasidone 80–200 mg/day or haloperidol 2.5 mg IM on entry, followed by 2.5–10 mg IM at 4–6 hourly intervals (maximum daily dose, 40 mg); then by oral haloperidol 10–80 mg/day. The mean number of IM injections administered was 3.9 for ziprasidone and 3.4 for haloperidol; the mean IM doses at the last injection were 11.7 mg and 4.6 mg, respectively. The mean reduction in BPRS at the last observation on IM treatment was numerically superior with ziprasidone (–6.2) compared with haloperidol (–3.2). This difference was maintained at endpoint. Ziprasidone was associated with a lower incidence of adverse events during IM treatment and during the entire study compared with haloperidol. Most notable was the lower incidence of movement disorders associated with IM ziprasidone. Anticholinergic therapy was administered to 14% of those on ziprasidone and 48% of those on haloperidol during the study. Simpson-Angus and Barnes Akathisia scores improved from baseline with ziprasidone at both the last observation on IM therapy and at endpoint in contrast to the marked deterioration observed with haloperidol. Similarly, the mean AIMS score improved with ziprasidone and deteriorated with haloperidol. The results of this study indicate that rapid-acting IM ziprasidone was effective in reducing the symptoms of acute, non-organic psychosis. Moreover, ziprasidone was better tolerated than haloperidol, particularly in assessments of movement disorders. The transition from IM to oral ziprasidone was well tolerated with further improvement in efficacy.

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ZIPRASIDONE IN THE LONG-TERM TREATMENT OF NEGATIVE SYMPTOMS AND PREVENTION OF EXACERBATION OF SCHIZOPHRENIA

M. Arato[1]*, R. O'Connor[2], J.E. Bradbury[3], H. Meltzer[4]. [1]*Kecskemeti u. 11, Budapest, H-1053, Hungary*
[2]*Pfizer Inc, New York, New York, NY 10017-5755;* [4]*Vanderbilt University Medical Center, Nashville, TN 37212, USA*
[3]*Central Research Division, Pfizer Inc, Sandwich, Kent CT13 9NJ, UK*

This prospective, randomized, double-blind, placebo-controlled study in chronically ill, stable patients living under medical supervision, compared ziprasidone 40 mg/day (n = 76), 80 mg/day (n = 72), 160 mg/day (n = 71) and placebo (n = 75) over 1 year in the prevention of acute exacerbation and treatment of negative symptoms of schizophrenia. Written, informed consent was obtained for all patients. Efficacy was assessed using the PANSS and GAF. To evaluate prevention of acute exacerbation, an end-point of impending relapse was prospectively defined. Patients meeting the criteria for impending relapse were withdrawn. Kaplan-Meier survival analysis demonstrated that the probability of experiencing an acute exacerbation at 1 year was significantly lower in the ziprasidone 40, 80, and 160 mg/day groups (40.5%, 34.6% and 35.8%, respectively) compared with placebo (70.8%; P = 0.003, P = 0.001 and P = 0.001, respectively). Ziprasidone was associated with a clinically and statistically significant improvement in negative symptoms over the course of the study compared with placebo ($P < 0.05$). There was a small early improvement with placebo with no change occurring after 6 weeks. By contrast, in patients treated with ziprasidone, negative symptoms generally continued to improve throughout the study. There was also a statistically significant improvement in positive symptoms and in PANSS depression factor with ziprasidone, and a substantial and significant improvement in GAF compared with placebo at 1 year. The tolerability of ziprasidone was excellent. Mean changes in movement disorder assessment scales with ziprasidone were indistinguishable from placebo. Ziprasidone was not associated with weight gain. This study demonstrated that ziprasidone provides long-term improvement in negative symptoms, prevents acute exacerbation of schizophrenia, is very well tolerated and improves global functioning.

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A COMPARISON OF RAPID-ACTING INTRAMUSCULAR (IM) ZIPRASIDONE 2 MG AND 20 MG IN PATIENTS WITH PSYCHOSIS AND ACUTE AGITATION

K.R. Reeves[1]*, R.H. Swift[1], E.P. Harrigan[1]. [1]*Central Research Division, Pfizer Inc, Groton, CT 06340, USA*

This 24 h, randomized, double-blind study compared the efficacy and tolerability of fixed-dose, IM ziprasidone 2 mg (n = 38) and 20 mg (n = 41) in hospitalized patients with psychosis and acute agitation. After the initial IM dose, up to three subsequent doses could be administered a minimum of 4 h apart, if required. Efficacy was assessed using the CGI and PANSS and the seven-point Behavioural Activity Rating Scale (BARS), a novel measure of agitated behaviour ranging from 1 (difficult or unable to rouse), through 4 (quiet and awake/normal level of activity), to 7 (violent, requires restraint). After each dose the BARS was rated every 15 min for the first hour, each 30 min for the next hour, then hourly until the next injection or endpoint. The mean AUC for BARS at 2 h and at 4 h after the first injection was significantly lower

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