group, has received a combination of antipsychotics with anxiolytics (benzodiazepine group). Control group was treated only with classic antipsychotics (fluphenazine, haloperidol). Testing of psychotic symptoms was realised with the Brief Psychiatric Rating Scale (BPRS) and anxiety was measured by Spielberger's State-Trait Anxiety Index (STAI). Obtained datas were pondered and presented numerically from 1.00 (without anxiety) to 3.00 (very high anxiety). Psychotic behavior was also presented numerically as psychotic index.

In both groups anxiety was at level of 2.96 index points before treatment (very high anxiety). In control group there was no significant improvement (2.38 at the end of examination) which indicates minimal improvement ($p = 0.10$). In experimental group which was treated with combine therapy (antipsychotics and benzodiazepines) there was significant improvement of anxiety, specially psychotic one ($r = 0.059$). This fact indicates very low anxiolytic potential of phenothiazines. Reduction of psychotic features in sense of partial remission of sch phenomenons is significant in both groups (from 178.4 to 46.3 index points, $p = 0.05$).

Hence anxiety in main dynamic force which has great influence at beginning and a development of sch process, polytherapy is necessary in treatment of these patients. It is consisted, in first place, of antipsychotics and anxiolytics, and very often antidepressive because of postschizphrenic depressive syndrome which occurs very often. In that way, it is possible to reach significant reduction of, not only psychotic anxiety but also free floating anxiety which always is present in pre psychotic and post psychotic period in most schizophrenic patients.

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WEIGHT GAIN ASSOCIATED WITH CONVENTIONAL AND NEWER ANTIPSYCHOTICS: A META-ANALYSIS

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A comprehensive literature search of English and non-English articles identified 78 studies which included data on weight change in more than one patient treated with a specific antipsychotic. For each agent, a meta-analysis estimated the effects of 10 weeks of treatment on body weight. The degree of weight change at 10 weeks was estimated by random effects regression. Except for molindone, antipsychotic treatment was associated with weight gain. Placebo was associated with a mean reduction of 1.68 kg. Among conventional agents, mean weight change ranged from a reduction of 0.41 kg with molindone to an increase of 3.25 kg with thioridazine, with an intermediate effect observed for haloperidol, an increase of 1.06 kg. Among newer antipsychotics, mean increases were as follows: clozapine 4.46 kg, olanzapine 4.15 kg, sertindole 2.92 kg, risperidone 2.10 kg and ziprasidone 0.87 kg. Insufficient data were available to evaluate quetiapine. Pairwise tests of differences between newer antipsychotics showed no significant difference between olanzapine and clozapine. Weight gain was significantly lower with ziprasidone compared with clozapine, olanzapine, risperidone and sertindole. There were also significant differences between clozapine and risperidone and olanzapine vs risperidone and vs sertindole. Both conventional and newer antipsychotics are associated with weight gain. Among newer agents, clozapine appears to have the greatest potential to induce weight gain and ziprasidone has the least. The differences among newer agents may impact upon the choice of treatment for some patients. Not only is weight gain undesirable because of associated health risks, but it may also cause non-compliance with antipsychotic therapy which predisposes patients to relapse.

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THE EFFECT OF TREATMENT WITH TYPICAL AND ATYPICAL NEUROLEPTIC DRUGS ON NEUROPSYCHOLOGICAL MEASUREMENTS IN PATIENTS WITH SCHIZOPHRENIA

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Neuropsychological measures (frontal lobe tests, conjugate lateral eye movements) were performed in sixteen patients with paranoid schizophrenia 1) during acute episode, before starting pharmacological treatment (PANSS 126 ± 24) and 2) during improvement, on maintenance dose of neuroleptic drugs (PANSS 62 ± 24). Eight patients were treated with typical neuroleptic (chlorpromazine, levomepromazine, fluphenazine, perphenazine) and eight - with atypical one (clozapine, olanzapine, ziprasidone).

In whole group, after alleviation of psychotic symptoms, the results of frontal lobe tests improved, and in case of Stroop test A and B, significantly so. There were no differences between typical and atypical neuroleptic drug as to the magnitude of such improvement.

During acute episode, schizophrenic patients exhibited excessive activation of left hemisphere in response to emotional and spatial questions (i.e. directed to right hemisphere), measured by CLEM method. During improvement, an increase of activation of right hemisphere was observed in response to these questions, at the expense of left hemisphere activation. Such increase, reflecting a regulatory action on hemispheric activation was significantly greater in patients treated with atypical neuroleptic drugs.

The results obtained suggest a possibility of improvement of some cognitive functions as well as regulation of activational asymmetry in schizophrenic patients with neuroleptic treatment, the latter may be more marked with atypical than typical neuroleptics.

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ZIPRASIDONE: *IN VIVO* EVIDENCE OF CENTRAL $5HT_{1A}$ AGONIST ACTIVITY

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Ziprasidone is a novel antipsychotic with a unique specificity for dopaminergic and serotonergic receptors. *In vitro* studies of cAMP accumulation indicate that ziprasidone is an agonist at $5HT_{1A}$ receptors. Since $5HT_{1A}$ receptor agonism is thought to contribute to reduced extrapyramidal side-effect (EPS) liability and enhanced efficacy against both negative and affective symptoms of schizophrenia, we investigated the *in vivo* $5HT_{1A}$ agonist activity of ziprasidone by measuring its effects on dorsal raphe cell firing and cortical dopamine release in the rat. Ziprasidone inhibited dorsal raphe firing with an ED_{50} of 300 μg/kg intravenous (IV) and its inhibitory effect was blocked by pre-treatment with the $5HT_{1A}$ antagonist WAY-100635 (10 μg/kg IV). Although the $5HT_2/D_2$ antagonist olanzapine also slowed unit activity (ED_{50} = 1000 μg/kg IV), this effect was not attenuated by WAY-100635, but was reversed by pre-treatment with the norepinephrine re-uptake inhibitor, desipramine (5 μg/kg IV). This is consistent with olanzapine's α_1 antagonist activity, low affinity for $5HT_{1A}$ receptors, and

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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

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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

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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

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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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