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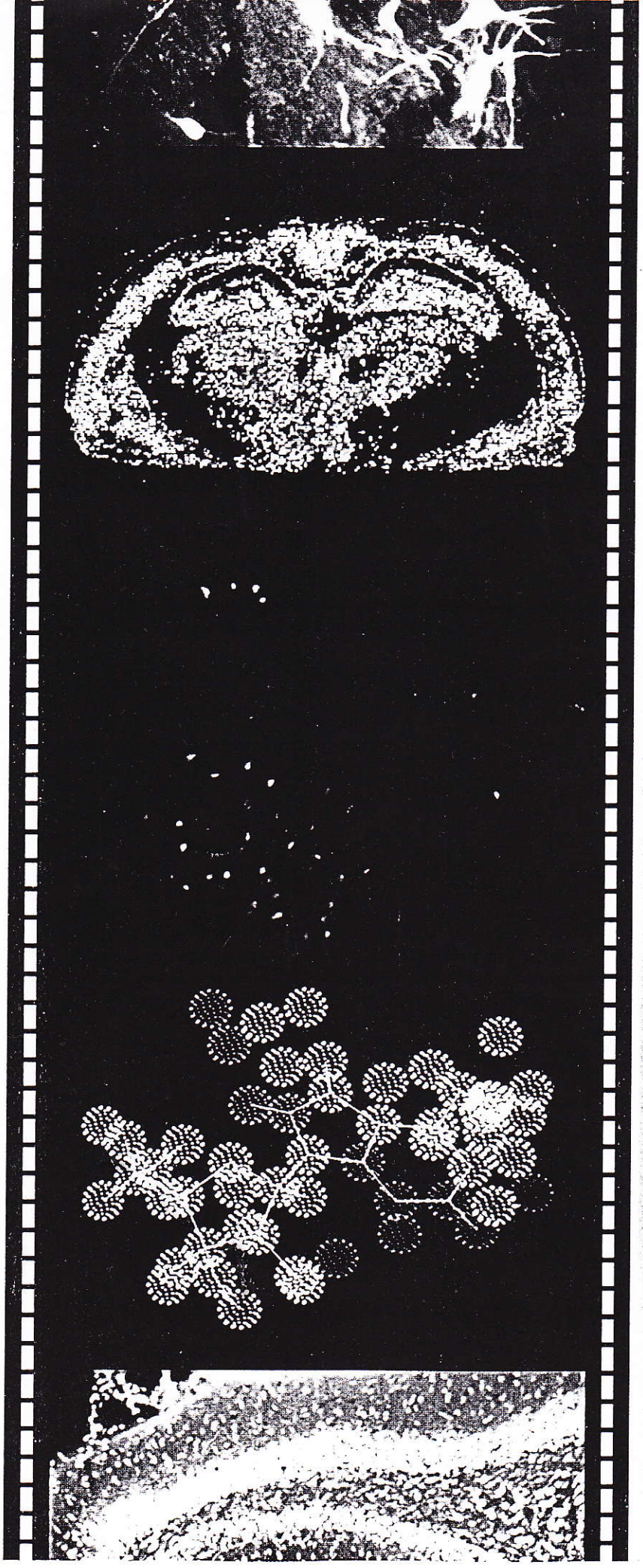

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ELSEVIER

080 Effects of single and multiple ascending doses of amisulpride in the pharmaco-EEG of healthy young male volunteers

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duction: The benzamide derivative amisulpride (AMI) n®) is registered for the treatment of acute and chronic phrenia. At low doses, AMI preferentially blocks pre- ic D2/D3 receptors, at higher doses it blocks post-synaptic ceptors in limbic structures. This study aimed at assessing dependent effects of AMI on the pharmaco-EEG.

thods: This was a double-blind, placebo-controlled, 3-way ver, dose-escalation study in 3 consecutive groups of 12 y male subjects. Subjects received amisulpride (AMI) at evels of 50mg (low), 200mg (medium) and 400mg (high) acebo once daily for 5 days. AMI and placebo periods separated by a washout of 7–21 days. EEGs were recorded low vigilance conditions and under high controlled vigilance ions on Days 1 and 5 pre-dose and 4, 8, 12 and ~25 hours ose. The EEG signal was digitalized and parametrized for te power in 7 standard frequency bands (1.5–30.0 Hz) and tal power. Data were evaluated using 3-way analysis of ce (ANOVA) with factors: subject, period and treatment ssessment, following tests for baseline heterogeneity. Pre- EEGs of each treatment period served as baseline for the is of post-dose changes. Effects were considered significant 0.05 (2-tailed) and are provided as mean differences and 95%-confidence intervals (C.I.).

ults and Discussion: Statistical tests for baseline het- neity did not reveal restrictions for the interpretation of ose differences. The main EEG change was a significant, related increase in theta power over placebo. After the low this change was only observed fronto-centrally at the 25-h ment after the final dose on Day 5. Following medium gh doses, theta power was already increased on Day 1. ay 5, this effect was seen fronto-centrally and occipito- rally. The maximum increase in theta power was already d with the medium dose of 200mg AMI. An increase in power is characteristic for neuroleptic drugs, in particular ing multiple high doses (Czobor and Volavka 1992, Small 987), and indicates disactivation and/or sedation. Although usness' ('inner restlessness') was the most frequent dose- dent adverse event in this study, EEGs revealed no consis- rsistent desynchronization. Other changes comprised some ious, scattered signs of stimulation such as increase in total (at both leads on Day 5). In a few subjects with severe sness/restlessness during medium or high AMI dosing, a d increase in slow beta and fast alpha frequencies was mainly on Day 5, as already reported from previous studies gle doses up to 100mg. However, the increase in theta toward Day 5 was also a predominant EEG change in these ual subjects.

clusion: The atypical antipsychotic drug AMI showed eristic EEG effects as soon as 200mg, and confirmed the onset of action observed in schizophrenic patients.

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P.2.081 Aripiprazole versus placebo in acute mania

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Objective: To compare the efficacy and safety of aripiprazole to placebo in patients with acute bipolar mania. Aripiprazole is a newly developed antipsychotic with a unique mechanism of action of potent partial agonism at D2 receptors, partial agonism at 5HT1A receptors, and antagonism at 5HT2A receptors.

Methods: This Phase III, multicenter, double-blind, placebo-controlled study randomized 262 patients with acute mania to aripiprazole 30 mg (which could be reduced to 15 mg if necessary) or placebo for 3 weeks. Patients remained hospitalized for a minimum of 2 weeks of the treatment phase. The primary measure of efficacy was the change in Y-MRS Total score. Response was defined as a decrease of $\geqslant$50% in Y-MRS Total score.

Results: Aripiprazole produced statistically significant improvements in Y-MRS Total score compared to placebo (−8.15 vs. −3.35, $p \leqslant 0.01$). In addition, the response rate was significantly higher in the aripiprazole group compared to the placebo group (40% vs 19%, $p \leqslant 0.01$). For all efficacy variables, aripiprazole separated from placebo by Day 4. Discontinuations due to adverse events did not differ between the aripiprazole and placebo groups, and there were no significant changes in body weight compared to placebo.

Conclusion: Aripiprazole is effective and well tolerated in the treatment of acute mania in patients with bipolar disorder.

P.2.082 Comorbid panic symptoms and relation with clinical correlates in schizophrenia

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Objective: Severe anxiety symptoms observed in patients with schizophrenia are similar to panic attacks (PA) and sometimes meet DSM-IV panic disorder (PD) criteria. However, there is a limited number of researches of comorbid panic symptoms in schizophrenia, reporting 28–63% of schizophrenic patients have PA. Some of the authors have suggested that panic attacks were related to higher doses of antipsychotic drugs. Comorbidity of PA and PD aggravate the symptoms of schizophrenia, makes the treatment more difficult and leads to a chronical course. The aim of this study was to investigate the prevelance of PA and PD in schizophrenia and the clinical features of schizophrenic patients with panic symptoms.

Method: Forty nine patients (23 women and 26 men) who met DSM-IV criteria for schizophrenia admitting to the psychiatric outpatient clinic between December of 2000 and May of 2001 were randomly included in the study. The mean age of the patients was 39,35+11,93 and mean duration of the disease was 16,00+10,54 years. The sociodemographic and clinical features were examined in a structured interview. PA and PD diagnoses

were confirmed by SCID-I. Positive and Negative Syndrome Scale (PANSS), Hamilton Depression Rating Scale (HADRS), Clinical Global Impression (CGI),and Extrapyramidal Symptom Rating Scale (ESRS) were administered to all patients. Bandelow Panic and Agorophobia Rating Scale was administered to the patients with panic symptoms. The statistical analysis were evaluated by chi-square and Mann Whitney-U tests.

Results: The patients with schizophrenia had 31% PA and 14% PD. The ratio of men who had PA or PD to the women who had PA or PD was 2/1 (p= 0,056). The patients with early onset (early than 18 years) had more frequent panic symptoms compared to the patients with late onset (P= 0,003). The patients with panic symptoms had higher scores of PANSS (P= 0,001), HADRS (p= 0,006), and CGI (p= 0,002).

Conclusion: The comorbidity of panic symptoms in schizophrenia aggravates the severity of the symptoms and leads to a worse clinical course.

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P.2.083 Meta-analysis of the safety and tolerability profile of aripiprazole in schizophrenia

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Objective: Aripiprazole is an antipsychotic with a unique pharmacologic profile: dopamine D2 partial agonism, serotonin 5HT1A partial agonism, and 5HT2A antagonism. Meta-analysis results of safety and tolerability are presented.

Methods: Five 4–6 week, double-blind, multicenter studies were conducted in 1,648 patients hospitalized with acute relapse of schizophrenia or schizoaffective disorder. Patients were randomized to aripiprazole (n=932), placebo (n=416), or active control (haloperidol 10 mg/day [n=201] or risperidone 6 mg/day [n=99]).

Results: Aripiprazole did not produce significant dose-dependent changes in Simpson-Angus or Barnes Akathisia scores compared to placebo. Haloperidol 10 mg produced statistically significant increases vs. placebo ($p<0.01$). Compared to placebo, aripiprazole was associated with an increase in body weight that was similar to haloperidol and less than risperidone. Aripiprazole did not result in increases in plasma prolactin levels that were different from placebo; however, haloperidol and risperidone both increased prolactin levels. Aripiprazole was not associated with QTc prolongation. The incidence of spontaneously reported somnolence with aripiprazole was comparable to placebo.

Conclusion: The favorable safety and tolerability profile of aripiprazole, including low potential for EPS, weight gain, prolactin elevation, QTc prolongation, and somnolence, suggests that aripiprazole is an important advancement in the antipsychotic armamentarium.

P.2.084 Meta-analysis of weight effects with aripiprazole

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Objective: A meta-analysis was done to assess the short- and long-term effects on weight gain (defined as a $\geq 7\%$ increase from baseline) of aripiprazole, a newly developed antipsychotic with a unique mechanism of action (dopamine D2 and serotonin 5HT1A partial agonism, and 5HT2A antagonism).

Methods: Short-term effects were assessed in five 4- to 6-week double-blind, controlled studies in 1,648 patients with schizophrenia or schizoaffective disorder, randomized to aripiprazole, placebo, or active control (haloperidol 10 mg/day or risperidone 6 mg/day). Long-term effects were assessed in a 52-week haloperidol-controlled study (n=1,294) and a 26-week open-label olanzapine-controlled study (n=255).

Results: In the short-term studies, aripiprazole was associated with a 0.7 kg increase in weight; haloperidol and risperidone produced 0.6 kg and 1.3 kg increases, respectively. In the long-term haloperidol study, patients with a baseline BMI <23 experienced weight gain with both haloperidol and aripiprazole, while patients with a BMI >27 experienced weight loss. At 26 weeks in the olanzapine-controlled study, aripiprazole resulted in an approximate 1 kg weight loss versus a 4 kg weight gain with olanzapine. Aripiprazole resulted in weight loss in all BMI categories and olanzapine resulted in weight gain in all BMI categories.

Conclusion: Aripiprazole is associated with minimal weight gain, which is comparable to haloperidol and less than olanzapine.

P.2.085 Aripiprazole: A dopamine-serotonin system stabilizer

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Objectives: Aripiprazole, a novel antipsychotic, has demonstrated rapid and sustained antipsychotic effect with an excellent safety and tolerability profile. A detailed review of its mechanism of action is provided.

Methods: The binding affinity and functional activity of aripiprazole at dopamine and serotonin receptors have been investigated using Chinese hamster ovary (CHO) cells expressing human recombinant D2, D3, 5HT1A, and 5HT2A receptors from rat P-11 cells.

Results: Aripiprazole bound with high affinity to D2, D3, 5HT1A, and 5HT2A receptors (Ki=0.45, 0.80, 4.4, and 3.4 nM, respectively). At D2 receptors, aripiprazole acted as a partial agonist with relative intrinsic activity less than that of dopamine. Likewise, aripiprazole exhibited partial agonism properties at 5HT1A receptors. At 5HT2A receptors, aripiprazole was shown to exhibit antagonist properties.