limbic as compared to striatal DA receptors in vivo. At low doses, amisulpride facilitates DA transmission via a selective blockade of presynaptic D_2-, D_3-receptors. Ami is active anti-psychotic compound effective at low doses for negative symptoms and at high doses for positive symptoms of schizophrenia. The CNS profile of multiple doses of a low dosage regimen of Ami (50 mg OD for 4 days) was assessed in a randomised, double-blind, 3-way crossover, placebo-controlled study carried out in 12 young sleep-deprived (for 36 h) subjects, using EEG and various measures of psychomotor and cognitive functions. Caffeine (slow release, 600 mg) was used as a positive reference.

Multiple doses of Ami 50 mg OD was devoid of any detrimental effects on EEG, psychomotor performance and cognitive function after total sleep deprivation (TSD). Trends and significant increase in EEG beta (12–40 Hz) power and decrease in subjective sedation, more pronounced at the end of the TSD suggest possible alerting effects of amisulpride. Caffeine significantly antagonizes the detrimental effects of TSD (increase in EEG beta waves, speed of reaction, sustained attention and reduction of subjective sedation) peaking 3 to 4 h after dosing.

In conclusion, the present results demonstrate that Ami 50 mg is able to partially antagonize the deleterious effects of TSD on EEG and subjective sedation. In addition, Ami 50 mg is devoid of any detrimental effects on psychomotor and cognitive performance after TSD, a situation well-known to amplify such effects if they exist. Moreover, some data suggests possible alerting effects of this slow dosage of Ami.

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AMISULPRIDE IN SCHIZOPHRENIA: POST-MARKETING SAFETY PROFILE

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Amisulpride is an atypical antipsychotic drug which selectively blocks mesolimbic dopaminergic D2/D3 pre and post-synaptic receptors. It proved efficacy in acute exacerbations of schizophrenia at doses from 400 to 800 mg/d and in patients with predominant negative symptoms at dose from 50 to 300 mg/d.

The case reports of adverse reactions collected spontaneously either by the manufacturer from 1986 to June 30th, 1997 or by French Health Authorities from 1995 to June 30th, 1997 are analysed. The total number of treatment days for this period is estimated to be more than 150 million.

425 cases were analysed using the most medically relevant reaction (395 directly reported to the manufacturer, 30 reported by Health Authorities). These cases concerned mostly expected reactions which are related to endocrine system (n = 116, usually due to hyperprolactinaemia), to nervous and psychiatric systems (n = 98, one third being extrapyramidal symptoms and tardive dyskinesia being exceptional) and to nutritional disorders, mainly weight increase (n = 26). In no cases of liver, haematological, cardiac nor skin disorders, a causal relationship with amisulpride could be definitively established: either another cause was identified or no sufficient information was available. Acute overdosage (n = 11, 4 leading to death) often with concomitant psychoactive drugs, led to disturbances of consciousness and various cardiac rhythm disorders. No relevant drug interaction was observed as expected from the absence of hepatic metabolism of amisulpride.

In conclusion, the available post-marketing surveillance data confirm that amisulpride appears as a very safe drug.

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IMPROVEMENT OF NEGATIVE SYMPTOMS IN ACUTE SCHIZOPHRENIA WITH AMISULPRIDE

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Negative symptoms are very disabling in chronic patients and one of the main limiting factors for rehabilitation. They are also apparent to a considerable degree in schizophrenic patients with acute exacerbations, where they are associated with positive symptoms and probably mainly secondary in nature. Newer antipsychotics and, to a lesser degree, standard neuroleptics improve these negative symptoms in acutely ill patients. Amisulpride, a D2/D3 specific antipsychotic with preferential limbic affinity, was efficacious in improving predominant negative symptoms in chronic schizophrenic patients.

Three studies in acutely ill schizophrenic patients (DSM III-R/IV) designed to prove antipsychotic efficcay, were analysed with respect to improvement of negative symptoms measured with the PANSS Negative subscale. A total of 738 patients were included in these short-term studies (4 to 8 weeks duration), 465 received amisulpride (AMI 400–1200 mg/d), 160 haloperidol (HAL 15–20 mg/d), and 113 risperidone (RIS 8 mg/d). The baseline PANSS Negative scores were between 23.8 $\pm$ 4.9 and 27.8 $\pm$ 8.1 across studies. AMI improved the PANSS Negative subscale scores from 6.9 to 9.6 points, HAL from 5.1 to 7.4, and RIS 5.3. When data from the 3 studies were pooled, AMI, at antipsychotic doses of 400 to 800 mg/d, was superior to the reference compounds: mean change from baseline AMI 7.9 (CI 95%: 7.0; 8.7), HAL + RIS 5.7 (CI 95%: 4.8; 6.6), difference between groups: 2.2 (CI 95%: 0.9; 3.4, $p < 0.05$).

These results indicate that amisulpride not only improves primary negative symptoms at low doses, but also negative symptoms in acute exacerbations at antipsychotic doses. This is a unique therapeutic profile with a broad spectrum of efficacy on positive and negative symptoms of schizophrenia.

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MAINTENANCE OF ANTIPSYCHOTIC EFFICACY WITH AMISULPRIDE: RESULTS OF A LONG-TERM STUDY VERSUS HALOPERIDOL

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Maintenance drug treatment in schizophrenia is of utmost importance for the management of the disease and the social functioning of the patients. New antipsychotics with good efficacy on positive and negative symptoms and good tolerability will be well accepted by patients, increase compliance and decrease relapse rates. The long-term efficacy and safety of amisulpride (AMI), a specific D2/D3 dopamine receptor blocker with limbic selectivity, was assessed in a 12-month open randomised study versus haloperidol (HAL) in schizophrenic patients with acute exacerbations (DSM III-R). A total of 488 patients was included in the study (AMI 370, HAL 118), 67% were male, mean age was 36.8 (AMI) and 39.6 years (HAL), mean duration of illness was 12 years.

A total of 322 patients (AMI 253, HAL 69) having reached at least a 20% improvement of their BPRS baseline total score after one month, were analysed with a survival method to test maintenance of efficacy. Patients having a response <20% BPRS baseline score on one of the following visits, dropouts and patients with missing data were considered as failures. Using this conservative

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approach, 59% of AMI patients and 55% of HAL patients maintained efficacy up to 12 months (Kaplan-Meier estimates, log rank 0.58). When time course of mean BPRS total scores of all patients (LOCF) was compared, AMI was superior to HAL from the third month of treatment. On an intent to treat basis, AMI was superior to HAL in total BPRS score (mean change from baseline 17.0 ± 15.8 vs 12.8 ± 15.5, $p < 0.01$), PANSS Negative subscore (mean change from baseline 7.1 ± 7.7 vs 3.7 ± 7.4, $p < 0.01$) and quality of life (all dimensions of the QLS). AMI provoked significantly less EPS than HAL and correspondingly less antiparkinson drugs were prescribed to AMI patients. Overall, AMI was safe and efficacious in the long-term treatment of schizophrenia.

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AMISULPRIDE IMPROVES AFFECTIVE SYMPTOMS IN ACUTE SCHIZOPHRENIA

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Affective symptoms are frequently associated with symptoms of psychosis in schizophrenic patients and represent together with negative symptoms a considerable burden for rehabilitation. Furthermore, suicide is a frequent complication of schizophrenia. Affective symptoms, measured with the BPRS anxiety/depression subscore (items: depressive mood, guilt feelings, anxiety, somatic concern), were assessed during four short-term studies in acutely ill schizophrenic patients (DSM III-R/IV). Amisulpride (AMI 400–1200 mg/d) was compared with haloperidol (HAL 15–20 mg/d, 2 studies), flupenthixol (FLU 15–25 mg/d) and risperidone (RIS 8 mg/d). A total of 870 patients were included, 535 treated with AMI, 160 with HAL, 62 with FLU and 113 with RIS. The mean duration of illness was about 10 years. The baseline scores of the BPRS anxiety/depression subscale varied between 11.1 ± 3.9 and 13.2 ± 4.5. Mean improvement of this subscore was 5.0 (CI 95%: 3.8; 6.1) and 4.5 (CI 95%: 3.5; 5.5) with AMI 400–800 mg/d versus 3.3 (CI 95%: 2.2; 4.4) and 3.1 (CI 95%: 2.0; 4.1) in the HAL groups (for both studies $p < 0.05$). In the study vs FLU, the improvement was 5.6 (CI 95%: 4.6; 6.6) for AMI and 3.6 (CI 95%: 2.6; 4.7) for FLU ($p < 0.05$). The improvement with AMI was also greater in the study vs RIS but this difference did not reach statistical significance: mean change AMI 3.2 (CI 95%: 2.5; 3.9) vs RIS 2.7 (CI 95%: 2.0; 3.5).

The results show that amisulpride improves affective symptoms more than the standard neuroleptics haloperidol and flupenthixol in acutely ill schizophrenic patients.

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AMISULPRIDE IN SCHIZOPHRENIA: A REVIEW OF ITS EFFICACY IN ACUTE AND CHRONIC PATIENTS

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Amisulpride (AMI) is a D2/D3 specific antipsychotic with limbic selectivity. Its efficacy has been demonstrated in both ptients with acute exacerbations of schizophrenia and in chronic schizophrenia with predominant primary negative symptoms. A total of 870 patients, 535 treated with AMI (100–1200 mg/d) have been included in four short-term studies to assess efficacy in acute schizophrenia (DSM III-R/IV) compared with haloperidol (HAL 15–20 mg, 160 pat.), flupenthixol (FLU 15–25 mg, 62 pat.) and risperidone (RIS 8 mg, 113 pat.). BPRS total score was the primary efficacy endpoint. Negative, affective and extrapyramidal symptoms were also measured. Pooling of data in this studies showed that AMI was at least as efficacious as the comparator drugs: mean change of BPRS total score in the pooled AMI patients was 21.7 (CI 95%: 20.2; 23.3) versus all comparators 16.7 (CI 95%: 14.9; 18.4). The difference between AMI and the comparators was significant 5.1 (CI 95%: 2.7; 7.4, $p < 0.05$). Another series of four studies was performed in chronic schizophrenic patients (DSM III-R) with predominant negative symptoms and absent or low grade of positive symptoms. This type of patient is particularly difficult to treat and a major challenge in the management of schizophrenia. A total of 514 pat. were included, 312 treated with AMI (50–300 mg/d) and 202 with placebo. In all studies AMI was significantly superior to placebo in the main efficacy variable, the SANS total score. The size of improvement reached from 31% to 42% of baseline in the AMI groups vs 8% to 23% in the placebo groups. Positive symptoms, parkinsonism and depression were of low intensity at baseline and did not change notably over time, so that an influence of these factors on the improvement of negative symptoms is improbable.

Overall, AMI provides a wide spectrum of therapeutic activity from acutely ill to chronic patients with predominant negative symptoms.

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AMISULPRIDE — LONG-TERM SAFETY

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In a multicentre, international, open randomised, long-term study, amisulpride (AMI) was compared with haloperidol (HALO). Patients with acute exacerbation of schizophrenia (DSM III-R) were treated for 12 months. A total of 488 patients were exposed to the study drug: 370 to AMI and 118 to HALO. Flexible doses of 200 to 800 mg/d (up to 1200 mg/d) were used for AMI and 5 to 20 mg/d (up to 30 mg/d) for HALO. At the end of the study, mean daily doses were: 605 ± 267 for AMI and 14.6 ± 7 mg for HALO.

Completers were 55% in AMI group and 48% in HALO group. The drop-out rate for safety reasons was higher with HALO (10.2% vs 8.1%). Incidences of open reporting of side effects were similar for both compounds. Extrapyramidal side effects were reported at a higher frequency in HALO group (40.7% vs 25.9%). Endocrine events were low for both drugs (4.1% AMI and 2.5% HALO), and weight increase was higher in AMI group (increase of >5% from basal weight: AMI 32% and HALO 18%).

Simpson Angus scale showed statistically significant differences in favour of AMI, either at the endpoint and at the maximal score ($p = 0.0001$). The difference was also observed with Barnes Akathisia scale at the endpoint ($p < 0.001$). Tardive dyskinesia (AIMS) was less induced by AMI ($p = 0.014$).

Prolactin levels were increased with both drugs, but higher levels were obtained with AMI. Neither AMI, nor HALO increased above 500 ms the QTc, and only 2 patients in AMI group had a QTc increase of at least 60 ms compared with baseline. Laboratory parameters did not show relevant differences between two drugs.

In conclusion, amisulpride showed similar incidence of adverse events compared with haloperidol but a better neurological side-effect profile. Safety in long-term exposure did not differ from that observed in short-term trials.

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