chotics in patients with chronic schizophrenia. Patients received risperidone (n = 1056; all patients from flexible-dose studies and patients receiving 4–8 mg/day from fixed dose studies), haloperidol (n = 473), or other antipsychotics (n = 703; e.g., haloperidol, levomepromazine, perphenazine, remoxipride, thioridazine, and zuclopenthixol).

At endpoint, the mean decrease from baseline in Positive and Negative Symptom Scale (PANSS) total scores was significantly greater for patients receiving risperidone (−20.9) than haloperidol (−14.3; $p < 0.01$) or other antipsychotics (−16.2; $p < 0.001$). Risperidone-treated patients also showed a significantly greater decrease in the positive ($p < 0.01$), negative ($p < 0.05$), and general psychopathology ($p < 0.001$) subscale scores than patients receiving haloperidol or other antipsychotics. Cluster scores for cognition, affective symptoms, anxiety, and hostility each improved significantly ($p < 0.05$) more for patients receiving risperidone than haloperidol or other antipsychotics.

Efficacy data on patients with an acute exacerbation were available from 7 trials in which patients received risperidone (n = 372), haloperidol (n = 120), or other antipsychotics (n = 285). At endpoint, the mean decrease from baseline in PANSS total scores was significantly greater for patients receiving risperidone (−24.7) than haloperidol (−19.8; $p < 0.05$) or other antipsychotics (−19.8; $p < 0.01$). Risperidone-treated patients also showed a greater decrease in positive symptom scores (−7.8) than those receiving haloperidol (−7.1; $p < 0.1$) or other antipsychotics (−6.3; $p < 0.01$).

These findings are consistent with Phase III trial results that show risperidone is more efficacious than haloperidol for controlling a broad spectrum of symptoms in schizophrenia.

Wed-P64

'SEROQUEL'®: EFFICACY IN IMPROVING MOOD, AGGRESSION AND HOSTILITY OF SCHIZOPHRENIA

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'Seroquel'® (quetiapine), an atypical antipsychotic, has been demonstrated in a clinical trial programme to be effective in the treatment of schizophrenia with no greater EPS than placebo across the full dose range of 150 mg–750 mg/day.

In clinical practice the treatment of depression, aggression and hostility pose particular challenges in management and these problems contribute to increased morbidity and impairment in quality of life.

We present an evaluation of quetiapine in treating the depressive, aggressive and hostile symptoms occurring in schizophrenia using data from four randomised controlled clinical trials. Symptoms were rated using Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression (CGI). A meta- analysis comparing quetiapine and placebo in treating affective symptoms was carried out on grouped change from baseline, using BPRS factor 1 score, a BPRS mood cluster, the BPRS depression cluster and the BPRS depression item. This analysis demonstrated that quetiapine was associated with a greater proportion of patients showing improvements in affective symptoms and fewer getting worse than with placebo.

Aggression and hostility were measured using BPRS Factor V score, BPRS hostility item and BPRS hostility cluster. In a multiple dose study, in which 5 quetiapine doses (75, 150, 300, 600, 750 mg/day) were compared with placebo and haloperidol (12 mg/day), beneficial effects on the measures of hostility and aggression were evident in the quetiapine groups but not the haloperidol group, reaching significance ($p \leq 0.05$) compared with placebo at doses of 150 mg, 300 mg and 600 mg/day.

These results provide initial evidence, that, in addition to being an effective antipsychotic, quetiapine may have a beneficial effect on low mood, aggression and hostility. This, combined with a favourable EPS and tolerability profile across the dose range, suggests that quetiapine will present a valuable first-line treatment for schizophrenia and other psychotic disorders and may offer an improved quality of life for schizophrenic patients.

Wed-P65

'SEROQUEL'®: A NEW OPTION FOR THE TREATMENT OF SCHIZOPHRENIA WITH NO GREATER EPS THAN PLACEBO

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EPS, especially akathisia, are distressing consequences of standard antipsychotic therapy, often leading to patient dissatisfaction and non-compliance. Therefore, confidence that increasing the dose of an antipsychotic will not lead to greater incidence of EPS is important. A clinical trial programme has demonstrated that 'Seroquel' (quetiapine), over a dose range of 150–750 mg/day, is an effective antipsychotic. Moreover, higher doses of quetiapine were associated with no more EPS than placebo.

We present are EPS data from 4 double-blind, placebo-controlled Phase II/III trials (quetiapine n = 510, placebo n = 206). The proportion of patients reporting EPS adverse events was no different with quetiapine [Q] (7%) than with placebo [P] (12%) and no statistical difference was seen in the proportion of withdrawals due to EPS (Q = 0.2%, P = 0.5%) or proportions of patients receiving anticholinergic medication (Q = 9%, P = 13%). A meta-analysis confirmed these results, demonstrating that there was no difference between quetiapine or placebo in the proportions of patients either showing an improvement (46% and 48% respectively) or worsening (15% and 16% respectively) of EPS as measured by the SAS. Similar results were seen in analyses of AIMS and Barnes Akathisia Scales. This favourable EPS profile has been confirmed in haloperidol-controlled trials in which quetiapine showed superiority over haloperidol irrespective of how EPS was assessed. Furthermore quetiapine showed good general tolerability with a similar withdrawal rate due to adverse events as placebo. There were no statistically significant differences in the proportions of patients on quetiapine and placebo developing clinically significant haematological changes or in effects on plasma prolactin. Quetiapine has good general cardiovascular tolerability: the incidence of clinically significant QTc interval (>500 msec) was lower with quetiapine (0.5%) than with placebo (1.3%).

These data provide reassurance for the clinician that, unlike some other new antipsychotics, the occurrence of EPS, across the full quetiapine dose range, is no greater than that seen with placebo and suggests that 'Seroquel' may be accompanied by a greater degree of patient acceptability.

Wed-P66

EFFECT OF A LOW DOSAGE REGIMEN AMISULPRIDE (50 MG/D) ON EEG, PSYCHOMOTOR AND COGNITIVE PERFORMANCE OF SLEEP-DEPRIVED, HEALTHY SUBJECTS

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Amisulpride (Ami), a substituted benzamide, binds selectively to the dopamine (DA) D_2- and D_3-receptors. It has higher affinity for

https://doi.org/10.1016/S0924-9338(99)80625-7 Published online by Cambridge University Press

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.

Wed-P67

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.

Wed-P68

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.

Wed-P69

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

https://doi.org/10.1016/S0924-9338(99)80625-7 Published online by Cambridge University Press