An Open-Label Study of Amisulpride in the Treatment of Mania

Eduard Vieta, M.D., Ph.D.; Salvador Ros, M.D.; José Manuel Goikolea, M.D.; Antonio Benabarre, M.D., Ph.D.; Ekaterina Popova, M.D.; Mercè Comes, P.S.N.; Jorge Capapey, M.D.; and José Sánchez-Moreno, Psy.D.

Received June 16, 2004; accepted Oct. 5, 2004. *From the Bipolar Disorders Program, Hospital Clinic, University of Barcelona, IDIBAPS (Drs. Vieta, Goikolea, Benabarre, Popova, Capapey, and Sánchez-Moreno and Ms. Comes); and the Hospital del Mar (Dr. Ros), Barcelona, Spain.*

The authors thank the Stanley Medical Research Institute for their continuous support. This study was also supported by grants C03/06 from the Red Centro de Investigación de Enfermedades Neurológicas IDIBAPS-Instituto de Salud Carlos III Redes Temáticas de Investigación Corporativa.

Corresponding author and reprints: Eduard Vieta, M.D., Clinical Institute of Psychiatry and Psychology, Hospital Clínic, University of Barcelona, Villarroel 170; 08036 Barcelona, Spain (e-mail: evieta@clinic.ub.es).

Background: Amisulpride is a selective D_2–D_3 antagonist that has been reported to be effective in the treatment of schizophrenia and major depressive disorder. However, no prospective study to date has assessed the effectiveness and tolerability of this compound in mania.

Method: Twenty DSM-IV–defined acutely ill manic bipolar patients with a Young Mania Rating Scale (YMRS) score of 20 or more entered this open, prospective, 6-week study. Assessments included the YMRS, the Hamilton Rating Scale for Depression (HAM-D), the Clinical Global Impressions Scale for Bipolar Disorder, Modified (CGI-BP-M), and the systematic report of adverse events. Amisulpride was added to other medications, but other antipsychotics were not allowed.

Results: Fourteen patients (70%) completed the study. Using last-observation-carried-forward (LOCF) analyses, amisulpride produced significant improvements on the YMRS ($p = .0001$), the HAM-D ($p < .0141$), and the overall ($p = .0003$), mania ($p = .0001$), and depression ($p = .0268$) subscales of the CGI-BP-M. The most common side effect was sedation (N = 5, 25%), but there were also some extrapyramidal symptoms, galactorrhea, insomnia, and agitation. The mean amisulpride dose was 680 mg/day (LOCF) and 786 mg/day in completers.

Conclusions: This first prospective study on amisulpride in the treatment of mania suggests that, despite the limitations of the open, observational design and small sample size, amisulpride may be effective and reasonably safe in the treatment of bipolar mania. D_2 and D_3 antagonism may be involved in the mechanisms of the therapeutic response to antipsychotics in mania.

(J Clin Psychiatry 2005;66:575–578)

Atypical antipsychotics are widely used now in the treatment of mania. Randomized, placebo-controlled clinical trials have supported the efficacy of aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone.[1] Clozapine has also been assessed in a number of open studies. However, amisulpride, an atypical antipsychotic with well-established efficacy in the treatment of schizophrenia, has never been tested in mania in a clinical trial, and there are no reports in the international literature about its use in manic patients, not even case series or small open studies.

Amisulpride is an atypical antipsychotic with D_2 and D_3 dopaminergic receptor specificity. At low doses, it increases dopaminergic transmissions by preferentially blocking D_2 and D_3 presynaptic receptors. At higher doses, it antagonizes D_2 and D_3 postsynaptic receptors, reducing dopaminergic transmission in the limbic system, but not the striatum.[2] Amisulpride has low affinity for other dopaminergic receptor subtypes, as well as for histaminergic and muscarinic receptors. What makes amisulpride different from other atypical antipsychotics is that it has no affinity for serotonergic or adrenergic receptors.[3]

A potential advantage of amisulpride over other antipsychotics is that it may be more efficacious against affective symptoms, as shown in several comparative trials versus haloperidol and risperidone.[4] Actually, this compound is the only atypical antipsychotic so far to show efficacy in unipolar major depression and dysthymia in controlled trials.[5] Another potential advantage is that it does not seem to cause significant weight gain, which is an important downside of clozapine and olanzapine and, to a lesser extent, quetiapine and risperidone.[6] The main tolerability is-

sues with amisulpride have to do with hyperprolactinemia and dose-dependent extrapyramidal symptoms, similar to the tolerability issues with risperidone.[7]

This is a preliminary, prospective, open study on the effectiveness and tolerability of amisulpride in mania. A randomized clinical trial is also ongoing to better ascertain this issue.

METHOD

Twenty acutely manic patients entered the study after receiving a full explanation of the procedure and giving their written consent to participate. The Hospital Clinic's Ethic and Research Board approved the protocol. The inclusion criteria were current DSM-IV diagnoses of mania and bipolar disorder, a need for antipsychotic treatment as assessed by the research clinician, and a Young Mania Rating Scale (YMRS) Spanish version[8] score of 20 points or more. Other antipsychotics were not allowed, but lithium, anticonvulsants, and benzodiazepines were maintained if the patient had already been taking them at the time of inclusion for at least 3 months. Only 3 patients had their lithium (N = 1) or valproate (N = 2) doses increased within the month prior to study entry.

Measures used to assess the effectiveness of amisulpride were the YMRS, the 17-item Hamilton Rating Scale for Depression (HAM-D) Spanish version,[9] and the Clinical Global Impressions Scale for Bipolar Disorder, Modified (CGI-BP-M).[10] The primary efficacy variable was the magnitude of reduction in YMRS score. Responders were defined as those patients achieving at least 50% improvement in YMRS scores from baseline. Remission was defined as achieving a CGI-BP-M score of 2 or less on both the mania and depression subscales.[10] Side effects were systematically assessed at each study visit.

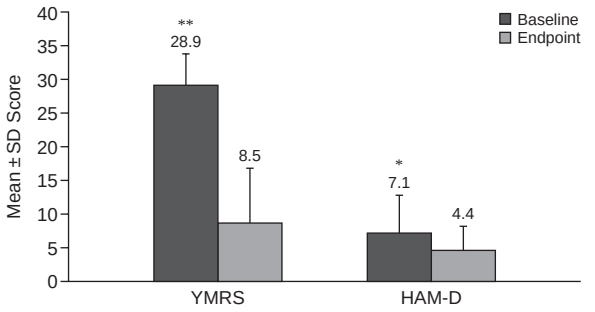
The study duration was 6 weeks. Assessments were performed at baseline and then at weeks 1, 2, and 6. All raters had previous experience in clinical trials and in the management of bipolar patients and had been trained in the use of the outcome measures. Analyses of efficacy were performed in an intent-to-treat approach. Scores on several rating measures were compared by means of the Wilcoxon and Friedman tests.

RESULTS

Patient Disposition

The number of patients who completed the 6-week follow-up was 14 (70%). The reasons for patient discontinuation were lack of efficacy (N = 2, 10%), side effects (N = 2, 10%), patient's decision (N = 1, 5%), and lost to follow-up (N = 1, 5%). Of the 2 patients who discontinued because of side effects, 1 reported insomnia and headache and 1 reported galactorrhea.

Figure 1. Baseline and Endpoint YMRS and HAM-D Scores During Treatment With Amisulpride



*p < .05.
**p = .001.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, YMRS = Young Mania Rating Scale.

The study enrolled 10 men (50%) and 10 women (50%) with a mean age of 43.9 years. Eight patients (40%) were treated as inpatients and 12 (60%) as outpatients. Seven patients (35%) had psychotic symptoms, and 3 (15%) had mixed mania at study entry. Comorbidities were alcohol abuse (N = 6, 30%), personality disorder (N = 5, 25%), anxiety (panic) disorder (N = 2, 10%), and cocaine abuse (N = 2, 10%).

Efficacy

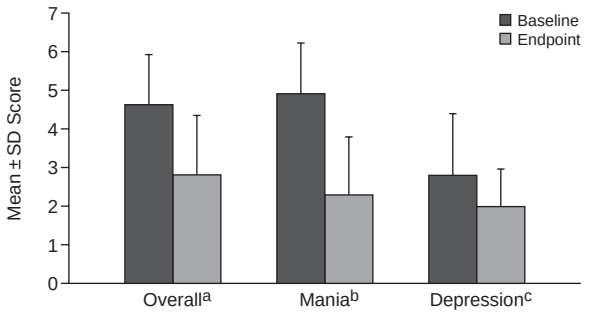
Treatment with adjunctive amisulpride was associated with significant improvement in mean ± SD YMRS scores at 6 weeks (baseline 28.9 ± 4.9, endpoint 8.5 ± 8.1; Wilcoxon z = –3.9199, p = .0001). Mean HAM-D scores significantly improved as well (baseline 7.1 ± 5.6, endpoint 4.4 ± 3.6; Wilcoxon z = –2.4548, p < .0141), as shown in Figure 1. Improvements in mean scores were also significant on the CGI-BP-M overall subscale (baseline 4.6 ± 1.3, endpoint 2.8 ± 1.5; Wilcoxon z = –3.6214, p = .0003), manic subscale (baseline 4.9 ± 1.3, endpoint 2.3 ± 1.5; Wilcoxon z = –3.8230, p = .0001), and depression subscale (baseline 2.8 ± 1.6, endpoint 2.0 ± 1.0; Wilcoxon z = –2.2151, p = .0268), as shown in Figure 2.

Thirteen patients (65%) were considered responders, as they achieved at least 50% improvement in their baseline YMRS scores. Remission was achieved by 10 patients (50%). When more conservative definitions of remission[11] were used, only 8 patients (40%) were in remission at study end. There were no differences in YMRS improvement in psychotic versus nonpsychotic patients (mean ± SD = 17.9 ± 7.6 vs. 21.8 ± 6.4; t = –1.24, p = NS).

Tolerability

Two patients discontinued because of tolerability issues (10%), including insomnia and headache in one pa-

Figure 2. Baseline and Endpoint CGI-BP-M Scores During Treatment With Amisulpride



[a]p = .0003, baseline vs. endpoint.
[b]p = .0001, baseline vs. endpoint.
[c]p = .0268, baseline vs. endpoint.
Abbreviation: CGI-BP-M = Clinical Global Impressions Scale for Bipolar Disorder, Modified.

Table 1. Adverse Events in Patients Treated With Amisulpride for Mania

Event	N	%
Sedation	5	25
Dry mouth	4	20
Insomnia	3	15
Galactorrhea	2	10
Tremor	2	10
Agitation	2	10
Anxiety	1	5
Dystonia	1	5
Akathisia	1	5

Table 2. Concomitant Medications in Patients Treated With Amisulpride for Mania

Medication	N	%
Clonazepam	10	50
Lithium	9	45
Valproate	7	35
Lorazepam	5	25
Carbamazepine	3	15
Topiramate	2	10
Flunitrazepam	2	10
Oxcarbazepine	1	5
Clorazepate	1	5

tient and galactorrhea in the other. The most commonly reported side effect was sedation (N = 5, 25%), followed by dry mouth (N = 4, 20%). Extrapyramidal symptoms included tremor (N = 2, 10%), dystonia (N = 1, 5%), and akathisia (N = 1, 5%). Table 1 shows the adverse events reported in this trial.

Although weight gain was not reported by the patients as an adverse event, there was indeed some slight weight increase (mean ± SD weight gain = 0.4 ± 0.9 kg), but only 1 patient (5%) gained more than 7% of body weight.

The combination of agitation and insomnia was seen in 2 patients (10%), one of whom also showed anxiety during the first week of treatment with amisulpride. This was successfully managed with a benzodiazepine (lorazepam).

Medication

Amisulpride was administered from day 1 to the endpoint using a relatively fast titration, which was individually decided upon by the investigators. The modal starting dose was 400 mg/day, the modal dose across the study was 800 mg/day, the mean ± SD dose (last observation carried forward) was 680 ± 262 mg/day, and the dose range was 300 to 1200 mg/day. By observed-case analyses, the mean amisulpride dose was 786 ± 241 mg/day.

Concomitant medication included a variety of drugs commonly used to treat bipolar disorder (Table 2), but no medication changes were allowed during the study except for amisulpride, lorazepam, and antiparkinsonian drugs. The mean ± SD benzodiazepine equivalent dose used was 11.75 ± 7.5 mg/day.

DISCUSSION

This is, to the best of our knowledge, the first prospective study on the effectiveness and tolerability of amisulpride in mania. A systematic literature search using MEDLINE (keywords used were *amisulpride*, *mania*, and *bipolar disorder*) revealed that there was no such study published at the time this study was conducted. Amisulpride has proved to be effective for schizophrenia[12] and also for depression and dysthymia.[5] It is quite surprising that such a drug, with proven efficacy against psychotic and affective symptoms and widely used by experienced psychiatrists, had not been tested formally in mania yet. This study is only a pilot experience, but it supports further research with amisulpride in mania.

As mentioned, this study has many limitations. The absence of a control group, randomization, and blinding, plus the use of other medications and the small sample size, are reasons for caution in the interpretation of the positive results. However, the study has the advantage of enrolling "real world" patients, with comorbid conditions, concomitant drugs, and very flexible dosage, which is rarely the case in controlled clinical trials.

The results show that amisulpride significantly improved manic and depressive symptoms after 6 weeks. If confirmed in placebo-controlled trials, these results would support the general statement that all antipsychotics are effective in the treatment of mania, as is the case for aripiprazole, haloperidol, olanzapine, quetiapine, risperidone, and ziprasidone.[1] Chlorpromazine, clozapine, and pimozide have also been studied, but not in large, placebo-controlled designs. The importance, however, of proving the efficacy of amisulpride is that this would give further support to the importance of the involvement of dopamine in the pathophysiology of

mania and the response to treatment. As amisulpride is a quite pure D_2 and D_3 antagonist, dopaminergic antagonism would be confirmed as an important mechanism for the improvement of manic symptoms.

Tolerability issues are generally well assessed in observational studies, and the side effects reported in this study are clearly consistent with the safety profile of amisulpride in patients with schizophrenia.[13] There was a relatively low rate of extrapyramidal symptoms. Sedation was the most common side effect, despite the fact that amisulpride is not a particularly sedating drug, but sedation and somnolence are frequently reported by manic patients as consequences not only of the side effects of the particular drug used, but also of the reduction of excitement of mania. Perhaps more important are the reports of galactorrhea, insomnia, and agitation. Prolactin-related side effects are not uncommon with amisulpride.[14] However, perhaps because of the short duration of this study, sexual dysfunction was not reported as a side effect. The management of agitation and insomnia may require benzodiazepines. These adverse events may be related to the course of illness or to the effects of the drug, but have also been reported with other atypical antipsychotics.[15]

The mean dose of amisulpride in this study was 680 mg/day (786 mg/day in completers), which is quite similar to the dose that has proved to be effective for acutely ill schizophrenic patients. Most manic patients were able to tolerate a starting dose of 400 mg/day, with only 1 case of hypotension. Exceptionally, some patients may require doses as high as 1200 mg/day.

In summary, this is the first prospective study to suggest that amisulpride is effective and tolerable in the treatment of mania. Despite the limitations of the open, observational design and small sample size, the study indicates that controlled trials are warranted and suggests that D_2/D_3 antagonism may be a relevant mechanism in the pathophysiology of the response to treatment in mania.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Thorazine, Sonazine, and others), clonazepam (Klonopin and others), clorazepate (Gen-Xene, Tranxene, and others), clozapine (Clozaril, Fazaclo, and others), haloperidol (Haldol and others), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), ziprasidone (Geodon).

REFERENCES

1. Vieta E. Atypical antipsychotics in the treatment of mood disorders. Curr Opin Psychiatry 2003;16:23–27
2. Curran MP, Perry CM. Amisulpride: a review of its use in the management of schizophrenia. Drugs 2001;61:2123–2150
3. Schoemaker H, Claustre Y, Fage D, et al. Neurochemical characteristics of amisulpride, an atypical dopamine D2/D3 receptor antagonist with both presynaptic and limbic selectivity. J Pharmacol Exp Ther 1997;280: 83–97
4. Peuskens J, Moller HJ, Puech A. Amisulpride improves depressive symptoms in acute exacerbations of schizophrenia: comparison with haloperidol and risperidone. Eur Neuropsychopharmacol 2002;12: 305–310
5. Lecrubier Y, Boyer P, Turjanski S, et al. Amisulpride versus imipramine and placebo in dysthymia and major depression. Amisulpride Study Group. J Affect Disord 1997;43:95–103
6. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004;27:596–601
7. Peuskens J, Bech P, Möller HJ, et al. Amisulpride vs risperidone in the treatment of acute exacerbations of schizophrenia. Amisulpride Study Group. Psychiatry Res 1999;88:107–117
8. Colom F, Vieta E, Martinez-Aran A, et al. Versión española de una escala de evaluación de la manía: validez y fiabilidad de la Escala de Young. Med Clin (Barc) 2002;119:366–371
9. Bobes J, Bulbena A, Luque A, et al. Evaluación psicométrica comparativa de las versiones en español de 6, 17 y 21 ítems de la Escala de valoración de Hamilton para la evaluación de la depresión. Med Clin (Barc) 2003; 120:693–700
10. Vieta Pascual E, Torrent Font C, Martinez-Aran A, et al. Escala sencilla de evaluación del curso del trastorno bipolar: CGI-BP-M. Actas Esp Psiquiatr 2002;30:301–304
11. Chengappa KN, Baker RW, Saho L, et al. Rates of response, euthymia and remission in two placebo-controlled olanzapine trials for bipolar mania. Bipolar Disord 2003;5:1–5
12. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 2003;60:553–564
13. Coulouvrat C, Dondey-Nouvel L. Safety of amisulpride (Solian): a review of 11 clinical studies. Int Clin Psychopharmacol 1999;14:209–218
14. Colonna L, Saleem P, Dondey-Nouvel L, et al. Long-term safety and efficacy of amisulpride in subchronic or chronic schizophrenia. Amisulpride Study Group. Int Clin Psychopharmacol 2000;15:13–22
15. Vieta E, Herraiz M, Parramon G, et al. Risperidone in the treatment of mania: efficacy and safety results from a large, multicentre, open study in Spain. J Affect Disord 2002;72:15–19