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Amisulpride versus fluoxetine in patients with dysthymia or major depression in partial remission

A double-blind, comparative study

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Abstract

In a multicentre, double blind, parallel group study 281 patients with DSM III-R diagnosis of dysthymia or a single episode of major depression in partial remission were randomised to 3 months of treatment with amisulpride 50 mg/day or fluoxetine 20 mg/day. The baseline Montgomery and Asberg Depression Rating Scale (MADRS) total score was reduced by at least 50% in 74.1% of patients (103/139) with amisulpride and 67.4% (87/129) with fluoxetine ($P = 0.230$). No significant differences between treatment groups were found in the reductions in mean total score with the MADRS, Widlöcher psychomotor retardation scale, Sheehan disability scale, and CGI. Anxiety measured by HAM-A total mean score decreased significantly more with amisulpride (63%) than with fluoxetine (54%; $P = 0.021$). There were 13 dropouts due to adverse events with amisulpride and ten with fluoxetine. The number of patients reporting at least one adverse event was similar in the two groups (amisulpride 47.5%; fluoxetine 40.9%). As expected, in the amisulpride group endocrine-like adverse events in female patients were the most common, while nausea, dyspepsia, anorexia and insomnia occurred more frequently with fluoxetine. © 1998 Elsevier Science B.V.

Keywords: Dysthymia; Major depression; Fluoxetine; Amisulpride

1. Introduction

Experimental studies on the aetiology of mood disorders have implicated a large number of central nervous system neurotransmitters, including norepinephrine, serotonin, acetylcholine and gamma-amino-butyric acid. However, a consistent set of data indicate that dopamine (DA) might play an important role in depression (Willner, 1995).

These findings point convincingly to a DA deficiency in syndromes characterised by psychomotor slowing, anhedonia, low energy and lack of motivation, and suggest that DA hypoactivity may be a

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[1]The author undertook this work on behalf of the Amiflu Study group. A complete listing of the Amiflu Study group can be found in appendix A.

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major factor in the pathogenesis of psychomotor retardation.

Amisulpride is an orthomethoxy-benzamide compound, chemically related to sulpiride, with higher affinity for the D_2/D_3 receptors in the limbic system than in the striatum. At low doses amisulpride preferentially blocks pre-synaptic D_2/D_3 autoreceptors thus increasing DA release (Coukel et al., 1996; Schoemaker et al., 1997). This compound shows higher affinity than sulpiride for dopaminergic receptors, particularly the D_2 sub-population. Its marked specificity of action has been confirmed in behavioural tests which have shown that amisulpride potentiated the hypermotility induced by DA agonists such as apomorphine (Carnoy et al., 1987; Guyon et al., 1993). This potentiation of DA-agonistic effects is taken to indicate a particular selectivity of action for the receptor populations in dopaminergic structures such as the nucleus accumbens and limbic cortex, for which amisulpride has greater affinity than other benzamides (Schoemaker et al., 1997; Perrault et al., 1997).

Dysthymia is a mild but chronic form of mood disorder, found to be associated with considerable social dysfunction and disability and at high risk for comorbidity (Akiskal, 1994; Robins et al., 1984).

Research indicates that tricyclic antidepressants (TCAs), the most recently introduced antidepressants, such as selective serotonin selective re-uptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) and reversible inhibitors (RIMAs) are efficacious in dysthymic patients (Harrison et al., 1986; Lecrubier et al., 1995; Rosenthal et al., 1992; Hellerstein et al., 1993; Ravindran et al., 1994; Baldwin et al., 1995; Dunner, 1996; Thase et al., 1996).

A dopaminergic molecule such as low-dose amisulpride could play a useful role in such a clinical condition, characterised by lack of energy, psychomotor retardation and depressed mood. In comparison with antidepressant drugs of other classes, amisulpride acts only on the dopaminergic system, whose reduced function appears to underlie many of the symptoms of this disorder, while having none of the tricyclics' effects on other aminergic systems.

In clinical studies in dysthymia, amisulpride, at the dose 50 mg once a day, was significantly more effective than placebo (Costa and Silva, 1990; Boyer et al., 1992; Lecrubier et al., 1997) and as effective as sulpiride (Scarzella et al., 1990), amitriptyline (Agnoli et al., 1989), imipramine (Lecrubier et al., 1997) and amineptine (Boyer et al., 1992).

This study assessed the clinical efficacy and safety of amisulpride 50 mg/day compared with a SSRI, fluoxetine 20 mg/day, in patients with dysthymia or major depression in partial remission over a 3-month treatment period.

2. Patients and methods

2.1. Patients

The study was conducted in outpatients recruited in 19 Italian psychiatric centres, listed in Appendix A. Those eligible for inclusion were psychiatric outpatients of either sex aged between 18 and 70 years, who met DSM III-R (American Psychiatry Association, 1980) criteria for dysthymia (code 300.40) or a single episode of major depression partial remission (code 296.25), taken as constituting a diagnostic equivalent of dysthymia. Each patient had to present a total score on the Montgomery and Asberg Rating Scale-MADRS (Montgomery and Asberg, 1979) between 14–26 points at the screening visit.

The following were exclusion criteria: experience of inefficacy or intolerance to the study drugs; suicidal risk or history of suicide attempts in the previous 2 years; abuse of or dependence on psychoactive substances as defined by the DSM-III-R; use of antidepressant agents or any psychoactive drugs in the 2 weeks before the trial; discontinuation of continuous or occasional use of benzodiazepines in the 2 weeks before recruitment; need for psychoactive agents other than the study drug during the trial. Patients were eligible if they had been taking a sleep-inducing drug for at least 2 weeks continuously in the recommended dose range as long as they continued that regimen throughout the trial without changing the dose. Other exclusion criteria were: severe debilitation; clinically relevant concomitant diseases not adequately managed by current therapy; cancer; pheochromocytoma; parkinsonian syndrome; ascertained or presumed pregnancy; breast feeding;

women of reproductive age not taking adequate contraceptive measures; previous evidence of poor compliance; participation in a clinical trial in the previous 6 months.

2.2. Ethics

This study was conducted in compliance with the declaration of Helsinki. The protocol was approved by the European Ethical Committee (Leuven-Belgium) on December 12th, 1992, before the trial started. The protocol was approved by local ethics committees at each investigational centre. Before selection, each patient had to give written or witnessed informed consent.

2.3. Design

This randomised, double-blind, parallel groups trial comprised two phases: (i) a 1-week, single-blind, placebo run-in to exclude placebo responders and (ii) a 3-month, double-blind, active treatment period.

At baseline visit, patients had to present a total MADRS score of 14–26 points. Patients whose initial total MADRS score dropped $\geq 20\%$ after the placebo run-in were defined as placebo responders and withdrawn from the study. Patients still fulfilling the inclusion criteria were randomised to either treatment arm.

During the 3 months of active treatment each patient was required to take one capsule of the study drug every morning. Compliance was assessed at every visit by drug accountability. In addition, randomly at one of the follow-up visits a blood sample was collected. Plasma levels of the study drug were measured by an independent central laboratory.

The MADRS, the Widlöcher Depressive Retardation Scale-ERD (Widlöcher, 1980), the Hamilton Anxiety Rating Scale-HAM-A (Hamilton, 1959), the Clinical Global Impression-CGI (National Institute of Mental Health, 1976) were administered at baseline and after 14, 28, 60, and 90 days of treatment. Each patient completed the Sheehan Disability Scale (Sheehan, 1983) at baseline and on days 28 and 90.

Safety was assessed by administering a check-list for the evaluation of somatic symptoms (CHESS 84) (Guelfi and Pull, 1983), the Columbia University Rating Scale (extrapyramidal symptoms) CURS (Baas et al., 1993) and the CGI therapeutic index at each visit. Whenever possible, the same person made the baseline and follow-up ratings for each patient. Any untoward medical events were recorded throughout the study. Routine laboratory safety tests were done at baseline and at the end of the study.

2.4. Statistics

A complete descriptive analysis was done at baseline on all randomised patients in order to verify the homogeneity of the two groups.

2.4.1. Efficacy analysis

The intention-to-treat efficacy population comprised randomised patients who had taken at least one capsule of the study drug and had at least one evaluation under treatment.

A type I error $\alpha = 5\%$ was used to establish significance, and two-sided statistical tests were used. One-way ANOVA was carried out for quantitative variables. For ordinal categorical variables, the Cochran-Mantel-Haenszel test (CMH) was used with ridit scores.

Items missing from the psychiatric scales were estimated from the mean integer of the items for the group and the visit concerned if not more than 20% of the items were missing. The LOCF (Last Observation Carried Forward) method was used for dropouts and the last available assessment was analysed.

The primary efficacy end-point was the MADRS; therapeutic response was defined as a $\geq 50\%$ reduction from the initial total score. The proportion of responders was compared by the chi-squared test. Secondary efficacy end-points were assessed by comparing differences from baseline in the various rating scales (MADRS, HAM-A, ERD, Sheehan Disability Scale). Between-group comparisons of MADRS and HAM-A profiles were assessed by three-way ANOVA (group, patient, visit) on the change from baseline. For each CGI item, the breakdown by class was given by treatment group at each visit.

The same efficacy analyses were repeated on the evaluable population, including only patients fulfilling protocol criteria.

2.4.2. Safety analysis

Safety analyses were carried out on all randomised patients who had received at least one dose. The incidence of adverse events was summarised for the active treatment groups according to the World Health Organisation adverse reaction terminology (World Health Organisation, 1994). In addition, adverse events were classified as treatment emergent adverse events (TEAE) and non-treatment emergent ones.

Changes from baseline at the last available visit and maximum changes from baseline at all evaluations during treatment were analysed using the CURS total score to assess extrapyramidal symptoms signs. The following were described for each treatment group as regards CHESS: (i) number of patients complaining of a symptom at baseline which worsened during treatment; (ii) number of patients who experienced a new symptom while on active treatment; (iii) number of symptoms and number of patients assessed at each visit for each treatment group. All worsened and new symptoms were taken into account independently from their relationship with study drugs.

Biological safety was assessed by checking all potentially clinically significant abnormalities (PCSA). Prolactin levels were not assessed.

3. Results

A total of 281 patients were included. The intention-to-treat analysis consisted of 268 patients (amisulpride 139; fluoxetine 129); 13 patients were not assessed as three of did not take any study medication and were lost to follow-up immediately after screening, and the remaining ten had no post-baseline evaluation.

Eighteen major protocol violations were detected: use of forbidden drugs in the 2 weeks before or during the study ($n = 2$); experience of inefficacy with fluoxetine ($n = 1$); poor compliance ($n = 9$); inconsistency between drug blood levels and randomisation ($n = 5$). Accordingly, the per protocol population consisted of 250 patients (amisulpride 133; fluoxetine 117).

A summary of demographic and diagnostic characteristics is provided in Table 1. Primary dysthymia accounted for 94% of the total population. Globally there were no significant differences between the two treatment groups with respect to age, sex, weight and body mass, race, alcohol use, medical history and concomitant treatments. The mean baseline MADRS, HAM-A, ERD, CGI (severity of illness), and Sheehan Disability scale score were not different in the two groups.

As shown in Table 2, overall 209 patients (78%) completed the 3-month treatment. Study completion rates and reasons for discontinuation were similar in the two groups.

3.1. Efficacy analysis

As the intention-to-treat analysis gave similar results to the per-protocol analysis, only the results of the first are reported in detail.

As shown in Table 3, the percentages of patients classified as responders, with a $\geq 50\%$ reduction of the initial mean total MADRS score, were 74% for amisulpride and 67% for fluoxetine. The difference was not significant (χ^2 test; $P = 0.230$).

Response rates to treatment in 253 patients with pure dysthymia resulted similar to those observed in global patient population: amisulpride 73% (96 out of 132 patients); fluoxetine 67% (81/121) (χ^2 test; $P = 0.316$).

Both drugs caused significant reductions in the total investigator-rated score (MADRS, HAM-A, ERD, CGI) and in the patient self-assessment scale (Sheehan Disability). At the last visit, the mean total MADRS score had fallen 62% in the amisulpride group and 56% with fluoxetine.

No statistically significant differences were found between the two drugs for the MADRS, ERD, Sheehan Disability scale, and CGI (global improvement at end-point).

For the HAM-A total scores, the mean ($\pm$S.D.) changes from baseline at last visit were 13.8 ± 8.2 for amisulpride and 11.5 ± 9.1 for fluoxetine the differ-

Table 1
Demographic and diagnostic characteristics of patients included in the intent-to-treat-analysis

	Amisulpride ($n = 139$)	Fluoxetine ($n = 129$)
Age Mean±S.D.	49.0±12.3	49.9±12.1
{range}	{19–70}	{19–70}
Sex ratio F/M	100/39	82/47
Profession		
Employed	41.2%	39.0%
Housewife	33.3%	38.2%
Retired	25.5%	22.8%
Alcohol use	27%	32%
Smoking	30%	27%
Previous or concomitant diseases		
Patients with at least one	51	47
Cardiovascular	37%	49%
Hepato-gastrointestinal	41%	26%
Neurological	12%	4%
Diagnosis		
Primary dysthymia (DSM III-R 300.4)	132	121
Single episode of major depression in partial remission	7	8
MADRS mean total score (±SD) at baseline	21.2±2.8	21.6±2.9
HAM-A mean total score (±SD) at baseline	21.4±6.5	21.6±6.6
ERD mean total score (±SD) at baseline	16.9±8.6	17.9±8.3
Sheehan Disability scale mean total score (±SD) at baseline	22.9±5.5	23.3±5.0
CGI-illness severity (moderately to markedly ill patients)	92.1%	89.1%
Concomitant treatment at baseline (No. of patients)		
Benzodiazepines	25	27
Non-benzodiazepine hypnotics	1	1

ence being significant ($P = 0.029$). This corresponded to 63% and 54% mean decreases in the total scores. No difference between groups was found about the concomitant use of anxiolytics. In fact, seven patients in both amisulpride and fluoxetine groups began a treatment with benzodiazepines during the trial.

Table 2
Reasons for discontinuation: randomised population

Reason for discontinuation	Amisulpride ($n = 142$)	Fluoxetine ($n = 139$)
Completed study	110 (77%)	99 (71%)
Total dropouts	32 (23%)	40 (29%)
Lack of efficacy	8 (6%)	9 (7%)
Adverse event	13 (9%)	10 (7%)
Lost to follow-up	6 (4%)	6 (4%)
Uncooperative	1 (1%)	5 (4%)
Other	4 (3%)	10 (7%)

3.2. Safety analysis

Safety analysis was done for 278 patients, exposed to at least one dose of either drug (amisulpride 141, fluoxetine 137).

Rates of discontinuation due to adverse events were similar: 13 out of 32 patients and 10 out of 40 patients in the amisulpride and in the fluoxetine group, respectively, dropped out because of an adverse event. Four patients discontinued amisulpride on account of endocrine disorders (three cases of non puerperal lactation, one amenorrhea) while more patients dropped out in the fluoxetine group because of gastrointestinal disorders (4.4% vs. 1.4%).

Safety data are summarised in Tables 4 and 5.

In the amisulpride group, 67 out of 141 (47.5%) experienced at least one emergent adverse event and 56 out of 137 patients (40.9%) taking fluoxetine. All recovered spontaneously; the endocrine-like adverse

Table 3
Efficacy criteria: intent-to-treat analysis

	Amisulpride ($n = 139$)	Fluoxetine ($n = 129$)	P
MADRS			
Responders (total mean score reduction $\geq 50\%$ from baseline)	103 (74%)	87 (67%)	0.230
Baseline	21.2±2.8	21.6±2.9	
End-point	8.1±7.1	9.5±9.1	0.271
HAM-A			
Baseline	21.4±6.5	21.6±6.6	
End-point	7.7±6.8	10.1±9.4	0.029
ERD			
Baseline	17.0±8.6	17.9±8.3	
End-point	6.3±7.5	8.3±9.2	0.349
Sheehan disability			
Baseline	22.7±5.5	23.2±5.2	
End-point	12.5±7.1	12.9±8.2	0.897
CGI (global improvement at end-point)			
Much–Very much	109 (78%)	85 (66%)	
Minimally–No change	22 (16%)	33 (26%)	
Minimally–Much worse	8 (6%)	11 (8%)	0.302

Baseline and end-point values are total mean scores ±S.D.

events, in particular, disappeared after drug discontinuation.

Three serious adverse events were recorded. Two amisulpride-treated patients were admitted to hospital because of a relapse of dysthymia; amisulpride was discontinued and treatment with TCA was started. In both cases, the investigators excluded any causal relationship with the study medication. One fluoxetine-treated patient stopped taking the study medication after 45 days and went to the local hospital casualty ward because of persistent heartburn and dyspepsia; further investigations revealed a gastric cancer. The investigator excluded any relationship with the study drug.

Sixteen amisulpride-treated patients (12%) had a weight gain $\geq 5\%$, one (1%) lost $\geq 5\%$, and 122 (88%) had no significant change during treatment. Figures for fluoxetine were respectively 6 (5%), 6 (5%), and 116 (91%).

Neurological adverse events (hypertonia, hyperkinesia, dystonia, and tremor) were very uncommon, occurring in three patients in each treatment group.

No significant differences between groups were detected regarding extrapyramidal symptoms comparing total CURS score changes from baseline at each follow-up visit ($P = 0.542$) and maximum CURS changes from baseline ($P = 0.513$).

The percentages of patients reporting at least one worsened or new symptom during the study, according to CHESS 84, were comparable in the two groups ($P = 0.929$ and $P = 0.673$).

Overall, laboratory and cardiovascular safety tests did not show any clinically significant change after a 3-month exposure to the study drugs.

4. Discussion

Over the last 10 years a considerable number of studies have set out specific pharmacological treatments for dysthymia. This increase of interest could be explained by several, concomitant factors, including: (i) the association between chronic depressive symptoms and dysthymia with considerable impact social functioning; (ii) a better understanding that, for some patients, social dysfunction is a treatable symptom of a mood disorder rather than a result of character pathology; and (iii) the availability of new antidepressants characterised by fewer unpleasant side effects likely to lead to discontinuation (Friedman, 1993, Harrison and Stewart, 1993).

New agents include SSRIs, reversible inhibitors of monoamine oxidase type A, and DA-agonist benzamides.

The main purpose of this study was to compare two drugs, amisulpride and fluoxetine, able to interact with two different aminergic systems, dopaminergic and serotoninergic, in order to assess the clinical relevance of those two selective pharmacological approaches.

Amisulpride and fluoxetine were compared over a 3-month treatment period in a population of mostly dysthymic patients, with a preponderance of females and moderate depression at admission. Anxiety symptoms were widespread, as indicated by the mean HAM-A score of 21.

Patients' compliance to treatment was satisfactory in both groups, with a low and comparable propor-

Table 4
Treatment emergent adverse events: patients exposed to study drug

	Amisulpride ($n = 141$)	Fluoxetine ($n = 137$)
No. of patients reporting at least one TEAE[a]	67 (48%)	56 (41%)
Serious events	2	1
Most frequent TEAE ($\geq 2\%$)		
Weight gain	9.2	3.7
Nausea, Vomiting	0.7	8.8
Insomnia	7.1	8.1
Dry mouth	7.1	7.3
Anorexia	1.4	6.6
Somnolence	6.4	3.0
Loss of libido	6.4	1.5
Constipation	5.7	2.2
Headache	5.7	2.2
Fatigue	5.0	2.2
Dizziness	5.0	2.9
Amenorrhoea[b]	4.9	0.0
Lactation, non puerperal[b]	3.9	0.0
Dyspepsia	1.4	3.6
Increased appetite	2.8	0.0
Abdominal pain	2.8	1.5
Agitation	0.7	2.2
Abnormal accommodation	0.7	2.2
Sweating increased	0.7	2.2

[a] TEAE = Treatment Emergent Adverse Events.
[b] Only females (amisulpride 102; fluoxetine 87).

Table 5
CHESS 84 and CURS: patients exposed to study drug

	Amisulpride ($n = 141$)	Fluoxetine ($n = 137$)
CHESS		
Patients with at least one worsened symptom	45 (33.1%)	43 (32.6%)
Patients with at least one new symptom	92 (65.3%)	92 (67.7%)
CURS		
Mean ±SD at baseline	3.4±4.4	4.3±5.5
Mean ±SD change from baseline at end	1.8±3.3	2.1±3.8
Mean ±SD maximum change from baseline	2.1±3.1	2.4±4.0

tion discontinuing on account of either lack of efficacy or intolerance. Response to study medication was high and of the same order as the rates reported in recent studies with fluoxetine with a similar treatment duration (>8 weeks) but smaller samples (Dunner, 1996; Vanelle et al., 1997). The proportion of responders was slightly – but not significantly – higher with amisulpride. It would be interesting to assess whether patients not responsive to one drug respond more satisfactorily to the other one. The exclusion of the small sub-set of patients with major depression in partial remission did not alter the global results of the study.

The mean total MADRS score progressively de-

creased in both groups, to an average of ten after 2 months of therapy. Similarly, mean HAM-A score fell steadily under treatment, particularly in the amisulpride group, indicating that this benzamide, despite its activating properties, does not possess any anxiogenic effect.

Both compounds were well tolerated, as indicated by the low proportion of patients discontinuing the study because of intolerance. Overall, safety profiles of the two drugs were in line with previous findings and confirmed that fluoxetine is associated with a higher incidence of gastrointestinal disorders while amisulpride is more likely to induce endocrine-like disorders in women.

The lack of a placebo arm can be considered a methodological limitation. This decision was taken when the study was designed, on the basis of the low incidence of placebo responders observed in other studies (Boyer et al., 1992; Lecrubier et al., 1997; Hellerstein et al., 1993). However, the high response rates in both treatment groups cannot be attributed merely to a placebo effect.

The 3-month duration of this trial still constitutes a major limitation, although in previous studies with amisulpride (Boyer et al., 1992; Lecrubier et al., 1997) rates of improvement after 3 months and 6 months of treatment resulted similar. Further trials are needed to address the question of maintenance of response, believed to be clinically important in the therapeutic management of dysthymic patients.

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Appendix A

Investigators from the AMIFLU who participated in this study were:

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Research report

Amisulpride versus imipramine and placebo in dysthymia and major depression

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Abstract

Amisulpride, a selective antagonist of D_2 and D_3 dopamine receptors, acts preferentially on presynaptic receptors increasing dopaminergic transmission at low doses. In a multicentre, 6 months, placebo-controlled trial, amisulpride (50 mg/daily) was compared to imipramine (100 mg/daily) in the treatment of patients with DSM-III-R criteria for primary dysthymia, dysthymia with major depression or major depression in partial remission. A total of 219 patients were included. Both analyses (intention-to-treat and 'per protocol' analysis) detected significant differences between groups (active treatment vs. placebo) on all main rating scales (CGI, MADRS, ERD, and SANS). The number of patients reporting at least one adverse event was higher in the imipramine group than in the two other, mainly due to anticholinergic effects. Endocrine symptoms were more frequent in female patients treated with amisulpride. These results confirm the interest of a drug acting on dopaminergic transmission such as amisulpride in the treatment of depressed patients. © 1997 Elsevier Science B.V.

Keywords: Amisulpride; Dysthymia; Depression; Treatment; Placebo-controlled study

1. Introduction

Amisulpride is an *O*-methoxy-para-aminobenzamide which binds selectively to D_2 and D_3 dopaminergic receptors, but not to adrenergic, cholinergic, serotoninergic, or other receptors. This drug shows considerably greater binding to dopamine receptors located in the limbic system than to striatal receptors. Therefore, its activity is more important in the structures involved in affective behaviour than in those involved in motor behaviour. In mice and rats, amisulpride induces little sedation and inhibits motility only when given at high doses (10 to 100 mg/kg); the almost complete absence of cataleptigenic activity is consistent with the weak affinity of the compound for striatal receptors. In animals, low doses of amisulpride (up to 10 mg/kg) potentiate dopamine agonists and activate the central nervous system, probably because of the drug's preferential presynaptic binding (Scatton et al., 1994).

The therapeutic effect of amisulpride depends

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upon dosage. High doses of 400 to 1200 mg daily were required to control productive psychotic symptoms (Boyer and Puech, 1987). Lower doses ranging from 50 to 300 mg daily were significantly more effective than placebo in schizophrenic patients with predominantly negative symptoms (Boyer et al., 1995; Paillère-Martinot et al., 1995; Loo et al., 1996). Two placebo-controlled studies, of 93 and 125 subjects respectively, evaluated the efficacy of low doses of amisulpride (based on the hypothesis that increased dopaminergic transmission would alleviate anhedonia), in patients with chronic anhedonia, anergia and loss of interest, without psychotic or depressive diagnoses (RDC or DSM-III-R criteria). Amisulpride in a daily dose of 50 mg was significantly more effective than placebo in improving these symptoms (Lecrubier et al., 1988). Because patients with such chronic symptoms are likely to fulfill DSM-III-R criteria for dysthymia, it was decided to evaluate the efficacy of low doses of amisulpride in the treatment of this condition.

Earlier controlled treatment studies were conducted in patients with chronic minor depressive disorder, since dysthymia had not yet been defined (Paykel et al., 1982). Further clinical evidence supports the efficacy of different types of antidepressants in dysthymia: tricyclics (TCAs) (Kocsis et al., 1988), monoamine oxidase inhibitors (MAOIs) (Versiani, 1994; Lecrubier et al., 1995) and selective serotonin re-uptake inhibitors (SSRIs) (Hellerstein et al., 1993; Lapierre et al., 1994). All these compounds may interact on similar monoaminergic structures. Animal data suggest that increase of dopaminergic transmission in the nucleus accumbens may represent a final common pathway responsible for at least part of the spectrum of behavioural actions of antidepressant drugs (Willner, 1995). Moreover, convincing antidepressant effects have been reported with the directly acting dopamine agonist bromocriptine (Willner, 1995; Techar et al., 1981) and with the blocker of dopamine uptake, bupropion (Zung, 1983). Therefore, the comparison of a drug increasing exclusively dopaminergic transmission with a tricyclic antidepressant (acting on different monoaminergic transmitters) was both of theoretical and practical interest.

The aim of this study was to compare the efficacy and safety of amisulpride to imipramine (a TCA) and placebo in the treatment of dysthymia and major depression.

2. Material and methods

2.1. Design

This was a 6-month double-blind, randomized study conducted by 23 psychiatrists working in private practice in France comparing amisulpride with imipramine and placebo in outpatients.

A video training was performed before the trial to establish homogeneity between raters on efficacy scales.

The trial was conducted in compliance with the Declaration of Helsinki (1964), revised in Tokyo (1975). The patients gave their written informed consent prior to inclusion. The study protocol was approved by the Pitié-Salpétrière Teaching Hospital Ethical Committee, Paris.

2.2. Patient population

Male and female adult outpatients, fulfilling the following DSM-III-R (American Psychiatric Association, 1987) criteria: primary dysthymia; dysthymia with major depression of mild or moderate severity (double depression); or isolated chronic major depression in partial remission. The exclusion criteria were: (i) any other DSM-III-R diagnosis, (ii) risk of suicide, (iii) substance abuse, (iv) any severe somatic disease, (v) pregnancy or lactation, (vi) any contraindications to the use of either imipramine or amisulpride (including the administration of a monoamine oxidase inhibitor within 15 days prior to the start of the trial), (vii) administration within the previous month of any antidepressant in a daily dose higher than the equivalent of 50 mg clomipramine, and (viii) administration of either amisulpride or imipramine at any dosage within the last 3 months.

2.3. Treatment

Subjects were randomly allocated to the three treatment groups, with stratification by centre for diagnosis of major depression. They received respectively identical capsules of:

(i) amisulpride, as a single 50 mg capsule each morning.

(ii) imipramine, as one 50 mg capsule during the first week, and one 100 mg capsule each morning thereafter (This is the usual dosage for dysthymic outpatients in France).
(iii) placebo, as a single capsule each morning.

Treatment duration was 6 months. Subjects were considered evaluable if they completed at least 1 month of treatment.

Concomitant psychotropic medication was prohibited, with the exception of benzodiazepines at low dosage as hypnotic medication, when absolutely necessary (dosage up to 10 mg diazepam or equivalent).

A formal psychotherapy could not be initiated, but could be continued throughout the trial if initiated at least 6 months previously.

2.4. Assessment

Efficacy and safety assessments were made on days 0, 7, 28, then once a month or on the last day of treatment.

The primary efficacy criteria were the change in the total score of the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979), and the response rate using the Clinical Global Impression (CGI) rating (National Institute of Mental Health, 1976a). Patients were considered as responders when they were rated 'very much improved or much improved' at the last evaluation on the CGI 2. The evaluation on the Widlöcher Depressive Retardation Scale (ERD) (Widlöcher, 1983), Andreasen's Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983, 1990), Hopkins Symptom Checklist (HSCL) (Derogatis et al., 1974) and the Covi Anxiety Scale (CAS) (Lipman, 1982) were used as secondary criteria, in order to obtain additional information on the efficacy profile of amisulpride.

Safety evaluation was based on an open question on adverse events, the somatic symptoms scale of the Association for Methodology and Documentation in Psychiatry instrument (AMDP-5) (Bobon, 1983), the Abnormal Involuntary Movement Scale (AIMS) (National Institute of Mental Health, 1976b), the CGI and laboratory safety tests.

Standard laboratory safety tests were performed at baseline and after the end of the treatment (M6 or on the last day of treatment).

2.5. Treatment withdrawal

Treatment could be discontinued at any time in patients who showed deterioration or serious adverse events. Treatment withdrawal for lack of efficacy was permitted only after 28 days. In every case, the investigator was required to perform a comprehensive evaluation of the patient.

2.6. Statistical methods

Comparisons at baseline between groups used a one-way analysis of variance for quantitative variables; when treatment effect was globally significant, pairwise comparisons of treatments were done using the Student-Newman-Keuls procedure to look for between-group differences. For categorical variables, the three groups were compared with the chi-square test.

Between-group comparisons of quantitative data over time were performed using a two-way (stratum, treatment) analysis of covariance for the main efficacy variables and one-way analysis of covariance for safety variables; the dependent variable was the value after treatment and the covariate the value at baseline. When significant differences were found, pairwise comparisons between groups were performed using Fisher's lowest significant difference (LSD) procedure. Groups were also compared at each time-point (observed cases) using a one-way analysis of covariance with Fisher's LSD procedure to compare groups when overall significant differences were found.

Within-group comparisons of quantitative variables were performed using Student's *t*-test for paired data; for ordinal variables, Wilcoxon's test was used.

All the tests were two-sided. The alpha risk for the entire analysis was set at 5%.

The main efficacy analysis was an end-point analysis including all patients with no or only minor deviations from the protocol and a follow-up of at least one month (per protocol analysis). An intention-to-treat analysis in all study participants (including those who failed to meet eligibility criteria) was also performed.

3. Results

3.1. Patients

The initial sample was composed by 219 patients, including 73 patients in each of the three treatment groups. The demographic and clinical data are summarized in Table 1.

There were no significant differences between the three groups at baseline, except for minor differences in supine diastolic blood pressure without clinical relevance.

At baseline, scores of depression were fairly severe (mean MADRS score 25, mean CGI score 5.5, i.e. between markedly and severely ill) as could be expected for a population with chronic depression. The diagnoses are given in Table 1. No significant differences between groups at inclusion were found for diagnosis or mean scores on the rating scales.

There were 219 patients in the intention-to-treat analysis versus 156 included in the 'per protocol' analysis. Patients not respecting the protocol were as follows: 5, 7, and 4 patients in the placebo, imipramine, and amisulpride groups, respectively, were excluded as they did not fulfill the inclusion criteria (mostly with respect to previous treatment); another 16, 12, and 13, patients respectively were excluded due to deviations from the protocol (evaluations not performed within required dates), and finally one, three, and two patients respectively due to missing data at the 1-month (M1) assessment. The 63 patients excluded from the 'per protocol' analysis (but included in the intent-to-treat analysis) were compared with the 156 patients included, and were found to have higher severity scores only on the following HSCL factors: interpersonal sensitivity, depression anxiety, and somatisation. These differences probably resulted from some degree of personality disorder in this subgroup of 63 non-evaluable patients.

3.2. Premature discontinuation

A total of 118 patients completed the 6-months trial: 37 in the placebo group (51%), 38 in the imipramine group (52%) and 43 in the amisulpride group (59%).

Table 2 summarises the reasons for withdrawal in each of the three groups.

The highest early discontinuation rate occurred in the imipramine group due to adverse events (11 patients vs. none in the placebo and three in the amisulpride groups). The second highest rate was for inefficacy in the placebo group (seven patients vs. three in the imipramine and one in the amisulpride group).

The proportion of patients who were lost to follow-up was not significantly different in the three groups ($chi^2 = 0.26$, 2 df). Neither were there any significant differences for withdrawals due to improvement or for other reasons. In contrast, a highly significant difference was seen for withdrawals due to adverse events ($chi^2 = 14.45$, 2 df, $P = 0.001$), placebo vs. imipramine difference was significant. A significant difference for inefficacy/deterioration ($chi^2 = 14.88$, 2 df, $P = 0.001$), placebo vs. imipramine and placebo vs. amisulpride, was also seen.

Table 1
Demographic and clinical data

	Placebo ($n = 73$)	Imipramine ($n = 73$)	Amisulpride ($n = 73$)
Mean age (range)	42.9 (18–69)	44.0 (18–73)	41.8 (22–73)
Sex:			
% Male	39.7	52.1	43.8
% Female	60.3	47.9	56.2
% Unemployed	9.8	13.1	6.7
% Employed	65.6	50.0	55.9
% Married or cohabiting	56.2	57.5	45.2
Diagnosis (%)			
Primary dysthymia	42.5	39.7	41.1
Dysthymia with major depression	41.1	39.7	41.1
Major depresion in partial remission	16.4	20.5	17.8

Table 2
Withdrawals/premature discontinuation

Reason	Placebo	Imipramine	Amisulpride	Total	*P*
Inefficacy/deterioration	28 (21)	9 (6)	14 (13)	51 (40)	= 0.001
Adverse events	2 (2)	17 (6)	8 (5)	27 (13)	= 0.001
Improvement	1 (1)	2 (2)	4 (4)	7 (7)	ns
Other	5 (3)	7 (5)	4 (3)	16 (11)	ns
Total	36 (27)	35 (19)	30 (25)	101 (71)	

Late drop-outs in parentheses (last 5 months).

3.3. Efficacy

As the intention-to-treat analysis gave similar results compared with the 'per protocol' analysis, and most of the differences concerned only HSCL factors; only the results of the 'per protocol' analysis are reported in detail below. Table 3 gives the results of measures at baseline and end-point on the efficacy criteria.

In all comparisons concerning efficacy criteria, the two active drugs were significantly different from the placebo, but not from each other.

The proportions of responders (very much improved or much improved according to item 2 of the CGI at the last evaluation) were as follows: 33.3% (17/51) in the placebo group, 68.6% (35/51) in the imipramine group, and 72.2% (39/54) in the amisulpride group. Significant differences in the proportion of responders were seen between the imipramine and placebo groups ($P = 0.004$), as well as between amisulpride and placebo ($P = 0.0001$). However, no statistical difference was observed between the two active treatment groups. In the intention-to-treat analysis, the results were 34% (25/73), 63% (46/73), and 64% (47/73), respectively. At the end of the study, the recovery rate (MADRS scores equal or below seven) was as follows: 21.9% (16/73) in the placebo group, 32.9% (24/73) in the imipramine group and 35.6% (26/73) in the amisulpride group. This indicates that although global improvement was substantial in the two active treatment groups, a considerably smaller proportion of patients attains a state of remission, which could be explained by the chronic features of the disorder.

3.4. Time-course

The same profile of results was already observed after 4 weeks of treatment on observed cases for MADRS scores: the mean score was 18.74 in the placebo group, 15.70 in the imipramine group and 15.76 in the amisulpride group.The differences between the placebo and the imipramine group ($P = 0.008$) as well as between the placebo and the

Table 3
Efficacy criteria (MADRS, CGI, responders) ('per protocol' analysis)

	Placebo (P, $n = 51$)	Imipramine (I, $n = 51$)	Amisulpride (A, $n = 54$)	*P*
MADRS score				
Baseline	24.2	25.3	23.9	
End point	16.6	13.1	11.2	= 0.01 P/I = 0.032 P/A = 0.004
CGI severity score				
Baseline	5.6	5.5	5.6	
End point	4.7	3.8	3.6	< 0.001 P/I = 0.002 P/A < 0.001
CGI2 responders (*n*, %)	17 (33.3)	35 (68.6)	39 (72.2)	< 0.004 P/I = 0.004 P/A < 0.001

amisulpride group ($P = 0.016$) were statistically significant. Both active drugs were not different from each other. For CGI severity scores, the differences were not statistically significant between the three groups after 1 month of treatment: 4.91 in the placebo group, 4.45 in the imipramine group and 4.60 in the amisulpride group ($P = 0.18$).

The efficacy analysis showed that coexisting dysthymia and major depression did not influence the results (no significant effect of diagnosis, no interaction between diagnosis and treatment).

Patients with a diagnosis of double depression (i.e. fulfilling the criteria for dysthymia and for major depression episode of mild to moderate intensity) showed the same treatment responses as the other patients.

Table 4 gives the results of the additional efficacy criteria.

The CAS scale for anxiety and the obsession/compulsion, interpersonal sensitivity, and depression factors on the HSCL showed significant differences overall between the groups; in these comparisons, both active drugs significantly differed from the placebo. However, the results here differed in the intention-to-treat analysis: only for the interpersonal sensitivity and depression factors on the HSCL an overall significant difference between the groups was found (in the latter, only imipramine significantly differed from placebo). Baseline scores on the CAS were fairly low, indicating that anxiety was not prominent in these subjects.

Overall differences between the three groups were significant for all the factors of the SANS scale, except 'attentional impairment', this factor was low at baseline. For the 'avolition/apathy' factor ($P < 0.001$) and for the 'anhedonia/asociality' factor ($P = 0.02$), the amisulpride-placebo differences were highly significant, whereas the imipramine-placebo differences were only indicative.

3.5. Safety

Forty-three placebo patients (59.7%), 63 imipramine patients (87.5%), and 39 amisulpride patients

Table 4
Additional efficacy criteria ('per protocol' analysis)

	Placebo (P, $n = 51$)	Imipramine (I, $n = 51$)	Amisulpride (A, $n = 54$)	P
SANS				
Baseline	28.7	27.6	27.9	
End point	20.6	14.6	13.3	0.01
ERD				
Baseline	21.7	21.3	21.0	
End point	16.2	11.4	11.2	0.01
CAS				
Baseline	7.9	7.7	7.4	
End point	6.4	5.5	5.1	0.02
HSCL				
Somatisation				
Baseline	10.8	10	10.7	
End point	7.7	5.7	4.6	0.12
Obsession/compulsion				
Baseline	12	10.8	11.4	
End point	8.5	5.9	5.9	0.04
Interpersonal sensitivity				
Baseline	7.4	8	7.4	
End point	5.2	4	3.4	0.05
Depression				
Baseline	14.1	14	14.2	
End point	10	6.9	6.8	0.02
Anxiety				
Baseline	7.9	7.2	7.2	
End point	4.8	4.2	3.2	0.03

(53.4%) reported at least one adverse event during the study. The number of patients withdrawn for such events from each group respectively were: 2 (2.7%), 17 (23%), and 8 (11%).

The safety profile was as expected in the imipramine group: dry mouth, constipation and dizziness being the most common. In the amisulpride group weight gain, dry mouth, and headache were the most common. The distribution of adverse events showed a non-specific profile for the patients treated with amisulpride, similar to the placebo group, with the exception of endocrine symptoms, such as galactorrhoea, breast pain, and menstrual disorder. These symptoms appeared in seven out of 41 female patients (17%), compared with one out of 34 (3%) in the imipramine group, and one out of 43 (2%) in the placebo group.

Neurological symptoms were observed in six amisulpride patients (8%), eight imipramine patients (11%), and two placebo patients (3%). These were primarily tremor and akathisia, but the AIMS scores showed virtually no change between baseline and endpoint and no differences between the three treatment groups.

Nine patients were reported to have fulfilled the criteria for serious adverse events in the study: four in the placebo group, three in the imipramine, and two in the amisulpride group. Most of these were hospital admissions due to inefficacy or aggravation of symptoms, two others were admissions for intercurrent diseases. None of the events could be clearly attributed to the study treatments.

On the AMDP-5, there were significant differences between the groups for seven symptoms: excessive thirst (16 in the placebo group, 27 in the imipramine group, 14 in the amisulpride group; $P = 0.03$), dry mouth (15, 52, 15, respectively; $P < 0.0001$), constipation (19, 34, 15, respectively; $P = 0.002$), dizziness (19, 29, 10, respectively; $P = 0.002$), palpitations (12, 25, 11, respectively; $P = 0.008$), blurred vision (3, 22, 8, respectively; $P < 0.0001$), and micturition difficulties (0, 6, 1, respectively; $P = 0.01$). In every case, overall significant differences were ascribable solely to higher incidences in the imipramine group.

Overall, no clinically relevant laboratory results were found after treatment in all three groups. However, standing systolic blood pressure was lower in the imipramine group at the end of the study (119.7 mmHg) than in either the placebo group (123.6 mmHg; $P = 0.03$) or the amisulpride group (123.2 mmHg; $P = 0.01$).

On item 3 of the CGI the overall safety evaluation at completion of the trial disclosed a highly significant overall difference ($P < 0.0001$) between the three groups. Mean value was 1.25 with the placebo, 1.35 with amisulpride, and 1.93 with imipramine, where 1 indicated the absence of adverse events and 2 the presence of events slightly detrimental to the patient. Pairwise comparisons indicated highly significant differences between imipramine and placebo ($P = 0.0002$) and between imipramine and amisulpride ($P = 0.0001$).

3.6. Concomitant medication

Benzodiazepine use was similar in the three groups (40%, 37% and 33% for placebo, imipramine and amisulpride groups, respectively). Non-benzodiazepine hypnotic drugs were used significantly higher in the placebo and amisulpride groups (9 patients, 12%) than in the imipramine group (2 patients, 3%) ($P = 0.04$). The use of drugs to correct dryness of the mouth was significantly higher with imipramine (19 patients, 26%) than with either of the other two drugs, (1 patient, 1.5% and 2 patients, 3%) for placebo and amisulpride groups respectively ($P < 0.0001$). Cardiovascular agents were used significantly more often in the imipramine group (18 patients, 25%) than in either placebo (5 patients, 7%) or amisulpride (7 patients, 10%) groups ($P = 0.005$). Finally, laxatives were likewise used significantly more often in the imipramine group (12 patients, 16%) than in placebo (4 patients, 5.5%) or amisulpride (3 patients, 4%) groups ($P = 0.004$).

4. Discussion

This study, comparing placebo, imipramine and amisulpride, (a benzamide drug that is considered to have dopaminergic effects at low doses) was designed to provide evidence of efficacy in a population of outpatients with dysthymia (82%) or chronic major depression (18%). Since the persistence of chronic symptoms after treatment of an episode of

major depression is difficult to distinguish from early dysthymia, patients with dysthymia or with chronic major depression were included in the study. Among dysthymic patients, about 50% had double depression and 50% had pure dysthymia.

Three limitations of this study should be mentioned. First, the use of benzodiazepines was recorded in approximately one-third of patients, but this does not seem to have modified the therapeutic effects of the study drugs. The proportion of patients receiving benzodiazepines were not significantly different in the three groups, any bias due to this factor is likely to have been minimal. Secondly, the inclusion of ineligible patients and some major deviations from the protocol were rather frequent; although the bias related to this factor cannot be evaluated, excluded patients did not seem very different from the others. An intention-to-treat analysis was used to circumvent this problem, providing a comparison with the analysis of 'per protocol' patients. Finally, the imipramine dosage, which is lower than usual for major depressive patients (150 mg/daily), could be considered as insufficient, although, 100 mg/daily is the current imipramine dosage for depressive outpatients in France. In addition, the significant improvement of the imipramine group compared with placebo indicates the efficacy of this relatively low dose.

Despite these limitations, the results of the study give valuable information on the efficacy of amisulpride in dysthymic patients, strengthened also by the consistency of the results across different scales evaluating several dimensions. The outcome of this trial shows a global antidepressant effect of the active drugs, rather than a simple improvement in depressed mood. The three treatment groups were comparable regarding almost all variables at baseline, the predominance of female over male and the patients mean ages being as expected for patients with this type of pathology. The proportion (approximately 40%) of patients with a concomitant episode of major depression at inclusion (double depression) confirmed the view that many patients with dysthymia meet criteria for major depression at some time during the course of their chronic depressive condition (Seivewright and Tyrer, 1990).

Results of the two main efficacy analyses, i.e. the intention-to-treat analysis of all 219 enrolled patients and the end-point analysis of the 156 evaluable patients treated for at least 1 month, were very similar. Both analyses detected significant differences between placebo and amisulpride and between the placebo and imipramine, but not between the two active drugs. Thus, imipramine and amisulpride were both clearly different from placebo, in their efficacy for relieving symptoms. Response rates show that the improvement in the two active treatment groups was not only statistically significant, compared with placebo, but also clinically substantial.

Secondary variables were used as supportive measures and the scores on the CAS, HSCL and SANS scales also showed that both active drugs were effective in the amisulpride and imipramine groups.

These secondary variables were selected in order to obtain data for further description of the clinical profile of amisulpride and will be presented in a future publication.

The efficacy results found in this study confirm the results of other trials using imipramine in dysthymia (Kocsis et al., 1988) and amisulpride in non psychotic patients with chronic symptoms of anergia (anergia, fatigue and decrease of initiative) (Lecrubier et al., 1988). Patients with major depression and dysthymia (double depression) seem to respond as well as patients with only dysthymia. Similar results were observed in patients treated with clomipramine and moclobemide (Lecrubier et al., 1995).

Overall, there was no difference in efficacy between amisulpride and imipramine, and both active drugs were significantly better than placebo. Clinical improvement was not different for patients with double depression from those with dysthymia. However, the safety and tolerability profile was better with amisulpride than with imipramine. With the exception of amenorrhoea/galactorrhoea, which was more frequent with amisulpride, there was no difference between that drug and placebo. These findings indicate that a drug with a selective action on dopamine can improve symptoms of depression in a substantial and clinically meaningful way.

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