European Neuropsychopharmacology, 1 (1991) 113–121

ADONIS 0924977X9100164R

ENP 00023

Interest of a loading dose of milnacipran in endogenous depressive inpatients

Comparison with the standard regimen and with fluvoxamine

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(Received 20 December 1990)
(Revised, received 4 January, 1991)
(Accepted 18 February 1991)

Key words: Milnacipran; Fluvoxamine; Antidepressant; Loading dose; Endogenous depression; Major depression

Summary

A multicenter controlled study was designed to test the hypothesis that a loading dose of an antidepressant could shorten the latency of its clinical efficacy. Three parallel groups of about 40 endogenous depressive inpatients received either a loading dose of milnacipran (300 mg daily for 2 weeks and 150 mg daily during the 2 following weeks), the standard regimen of milnacipran in severe depression (200 mg daily for 4 weeks), or fluvoxamine (200 mg daily for 4 weeks). The duration of the study was 4 weeks, with assessments at baseline and after 4, 9, 14, 21, and 28 days of therapy by means of Montgomery and Asberg depression scale (MADS), the Hamilton depression scale, the Clinical Global Impressions (CGI), and a checklist of symptoms and side-effects. Results showed very similar evolution in the 3 treatment groups. In addition, the level of side-effects did not exhibit significant differences among the treatment groups, except for excitement-nervousness and akathisia which were more frequently reported with fluvoxamine. These results do not support the usefulness of a loading dose of an antidepressant such as milnacipran. They demonstrate however that milnacipran can be given at a 300 mg daily dose from the very first day of treatment with an excellent tolerance.

Introduction

One of the major drawbacks of antidepressant therapy is the latency between the initiation of the treatment and the improvement of depressed mood (Baldessarini, 1989; Rudorfer and Potter, 1989). It takes generally about 2 or 3 weeks before any significant change in depressive symptomatology can be noted (Baldessarini, 1989; Rudorfer and Potter, 1989). The reason for this delayed efficacy is still unclear. In animals, most tests pre-

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dictive of antidepressant properties use acute design with single injection; moreover, neurotransmitter uptake inhibition, the classical characteristic of tricyclic antidepressants, is manifest without any delay.

Several hypotheses have tried to explain the delayed clinical onset. On the biochemical level, this period of time could be necessary to induce a down-regulation of postsynaptic receptors (Bannerjee et al., 1977; Sulser, 1979). On the clinical level, it could also be due to a too low dose of antidepressants used in the beginning of the treatment. Classical antidepressants, such as tricyclics and monoamine oxidase inhibitors, make it necessary to progressively increase their dosage in order to minimize their side-effects.

Milnacipran is a new antidepressant selected for its equipotent inhibition of noradrenaline and serotonin uptake and its lack of effect at any postsynaptic receptor (Moret et al., 1985). We recently demonstrated the efficacy of milnacipran in two double blind comparisons with amitriptyline in severely depressed inpatients (Ansseau et al., 1989a,b). The tolerance of milnacipran was excellent, with much less drowsiness and anticholinergic side-effects than with amitriptyline. Interestingly, a significant relationship was noted between the 3 daily doses of milnacipran used in these studies (50, 100, and 200 mg), the rate of clinical efficacy, and the rapidity of improvement (von Frenckell et al., 1990).

In this context, the purpose of the present study was to test if a loading dose of a well tolerated antidepressant, such as milnacipran, could shorten its clinical onset. We therefore decided to compare a loading dose of milnacipran (300 mg during 2 weeks) with the standard regimen of the same compound in severe depression, and with fluvoxamine, another recent antidepressant exhibiting an excellent profile of efficacy and tolerance (Benfield and Ward 1986). This approach could shed some light on the pathophysiology of the latency of antidepressant therapy and give some indications on the possibility of diminishing it.

Subjects and methods

Design of the study

The study was performed between January and September 1989 in nine Belgian centers used to collaborate and exhibiting good reliability in clinical rating (see affiliations). The trial used a double-blind design with 3 parallel groups of patients randomly assigned to milnacipran 300 mg/d for 2 weeks followed by 150 mg/d for 2 weeks, milnacipran 200 mg/d for 4 weeks, or fluvoxamine 200 mg/d for 4 weeks. The total daily dose was administered from the first day of the study in 2 equal daily intakes, morning and evening. The active period was preceded by a washout period of 4–7 days on placebo and lorazepam (up to 10 mg/d) and nitrazepam (up to 10 mg/d) if needed. These associated drugs could be maintained during the treatment period if necessary. The duration of the study was 4 weeks, with assessments at baseline (T0), and after 5, 9, 14, 21, and 28 days of treatment. The trial was monitored according to all principles of French and US 'good clinical practice' (Ministère des Affaires Sociales et de l'Emploi, 1987; Mathieu, 1990).

Subjects

One hundred and twenty seven inpatients were included in the study, 7 of whom were not included in the statistical analysis of efficacy for early drop-out (before day 14) or for nonrespect of the protocol (see Table 2). Therefore, the milnacipran 300–150 group comprised 41 patients, the milnacipran 200 group 42 patients and the fluvoxamine group 37 patients. Patients were 38 males and 89 females, aged 20–70 years, with a mean age (SD) of 43.7 (12.4) years. All subjects were severely depressed inpatients who fulfilled Research Diagnostic Criteria (RDC) for a definite major depressive disorder, endogenous subtype (Spitzer et al., 1978) and had a score of at least 25 on the Montgomery and Asberg depression scale (MADS) (Montgomery and Asberg 1979), a score of at least 5 (markedly ill) for the severity of illness as defined by the Clinical Global Impressions (CGI) (Guy, 1976), and a score on the Raskin scale for depression higher than the score on the Covi scale for anxiety (Raskin et al., 1967; Covi et al., 1979). Initial scores ranged from 25 to 58 with a mean (SD) of 36.3 (7.5) on the MADS and from 18 to 58 with a mean (SD) of 32.8 (8.0) on the 24-item Hamilton depression scale (Guy and Bonato, 1970; Pull, 1990), corresponding to 28.6 (7.9) on the 17-item version (Hamilton, 1960). Patients presenting any evidence of contra-indications for a tricyclic antidepressant, or

TABLE 1

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE SAMPLE AND FREQUENCY OF RDC SUBTYPES OF MAJOR DEPRESSION

	Milnacipran 300/150 group (n = 42)	Milnacipran 200 group (n = 44)	Fluvoxamine group (n = 41)	F/χ^2	P
Age (SD)	49.9 (12.4)	46.5 (13.3)	46.6 (11.2)	1.05	NS
Gender (M/F) (%)	33.3 / 66.7	31.8 / 68.2	24.4 / 75.6	0.91	NS
Weight (SD)	66.4 (10.7)	67.2 (12.9)	66.3 (14.0)	0.99	NS
Family history (%)					
depression	50	57	55	0.43	NS
mania	5	20	2.5	0.50	NS
Number of previous depressive episodes (SD)	3.9 (2.7)	3.5 (2.2)	3.3 (3.8)	0.41	NS
Length of depressive illness (years) (SD)	12.3 (7.3)	12.3 (8.7)	10.9 (8.0)	0.38	NS
Length of current episode (days) (SD)	62.9 (77)	78.7 (151)	62.7 (66)	0.32	NS
Presence of precipitating event (%)	14	36	24	1.32	NS
Previous therapy for current episode (%)					
antidepressant	19	24	27	0.71	NS
anxiolytic	67	51	64	2.81	NS
RDC subtypes (%)					
primary/secondary	93/7	91/9	92/8	1.08	NS
recurrent unipolar	86	86	67	1.61	NS
bipolar	14	4	7	2.86	NS
psychotic	9	14	9	2.22	NS
incapacitating	93	81	81	4.80	NS
endogenous	100	100	100	5.78	NS
agitated	26	36	34	0.90	NS
retarded	71	68	66	1.12	NS
situational	14	28	19	2.34	NS
Predominant mood					
mainly depressed	83	75	68	8.87	NS
mainly apathetic	17	18	32		
others	0	7	0		

serious or uncontrolled medical illness, were excluded from the study. The demographic and clinical characteristics of the patients are presented in Table 1. No statistically significant differences existed among the treatment groups.

All patients remained hospitalized for at least the first 2 weeks of treatment. The protocol obtained the approval of the Ethical Committee of the University of Liège Medical School, and all patients were fully informed of the purpose of the study and gave their consent.

Assessments

All assessments included the MADS, the 24-item Hamilton depression scale, the CGI, and a checklist of symptoms and side-effects which comprises specific items as well as reserve items related to behavior, central nervous system, autonomic nervous system, and miscellaneous rated as 0 (none), 1 (mild), 2 (moderate), and 3 (severe) (see Table 3). Pulse and blood pressure in the supine and standing positions were also measured. An ECG was performed before treatment and 2 weeks later, whereas laboratory tests, including hepatic and renal balance-sheets, were carried out before treatment and at the end of the treatment period.

Data analysis

Initially, the homogeneity of the 3 treatment groups was controlled, using analysis of variance (ANOVA) or chi-square statistics, eventually corrected by the Yates test for small samples. No significant differences were present related to age, weight, height, gender, civil status distribution, the 3 scores on the Raskin and Covi scales, scores on the MADS and Hamilton scales, frequency of RDC subtypes of major depression, previous psychotropic treatments, and personal and family psychiatric history.

All changes over time in ratings were assessed by ANOVAs with repeated measures. A second analysis was also performed reporting the endpoint scores for subsequent evaluations of patients who did not complete the 4-week protocol, but since the conclusions were similar, they are not reported in this

TABLE 2

REASONS AND DATES OF DROPOUT IN THE 3 TREATMENT GROUPS

Milnacipran 300/150 group	Milnacipran 200 group	Fluvoxamine group
dysuria: day 5	nonrespect of inclusion criteria: day 5	digestive symptoms: day 5
inefficacy: day 14	digestive symptoms + dermatitis: day 9	digestive symptoms: day 9
dysuria: day 14		digestive symptoms: day 9
paranoid delusions: day 14		digestive symptoms + manic switch: day 9
refusal of the patient: day 15		digestive symptoms: day 14
inefficacy: day 21		inefficacy: day 21
palpitations with extrasystoles: day 21 hypotension and syncope: day 24		

TABLE 3

COMPARISON OF THE FREQUENCY (PERCENTAGES) OF SIDE-EFFECTS

	Milnacipran 300/150 group (n = 42)	Milnacipran 200 group (n = 44)	Fluvoxamine group (n = 41)	χ^2	P
Adverse behaviour effects					
insomnia	11.9	15.9	17.1	0.20	NS
drowsiness	11.9	13.6	17.1	0.89	NS
excitement-nervousness	19.0	13.6	39.0	6.28	0.04
depression	4.8	2.3	12.2	3.12	NS
confusion	0	0	0	0.00	NS
others	2.4	2.3	2.4	0.00	NS
Central nervous system					
rigidity	0	0	0	0.00	NS
tremor	19.0	18.2	17.1	0.06	NS
dystonic symptoms	4.8	4.5	2.4	3.53	NS
akathisia	2.4	0	9.8	5.04	0.08
others	7.1	4.5	2.4	1.03	NS
Autonomic nervous system					
hypotension	31.0	20.5	19.5	2.24	NS
syncope	4.8	0	0	4.11	NS
tachycardia-palpitations	21.4	18.2	14.6	0.49	NS
nasal congestion	4.8	11.4	4.9	2.40	NS
dry mouth	26.2	31.8	29.3	0.75	NS
increased salivation	0	4.5	0	4.26	NS
blurred vision	16.7	15.9	24.4	0.65	NS
nausea or vomiting	35.7	38.6	53.7	2.71	NS
diarrhoea	14.3	9.1	17.1	0.74	NS
constipation	26.2	18.2	26.8	0.08	NS
urinary disturbances	7.1	6.8	4.9	0.21	NS
Miscellaneous					
dermatitis-allergy	4.8	2.3	4.9	0.36	NS
headache	23.8	20.5	26.8	0.71	NS
lightheadedness, dizziness, faintness, weakness	23.8	25	29.3	1.23	NS
weight gain, excessive	4.8	2.3	0	2.11	NS
weight loss, excessive	23.8	20.5	17.1	0.91	NS
others	14.3	18.2	12.2	0.22	NS

paper. All ANOVAs with repeated measures were followed by time-by-time ANOVAs associated with Bonferroni tests in order to complete the comparison between groups at intermediate times. All statistical procedures used a SAS package.

Results

Drop-outs

A total of 16 patients (12.6%) did not complete the study for nonrespect of the inclusion criteria, lack of efficacy or side-effects: 8 (19.0%) in the milnacipran 300–150 group, 2 (4.5%) in the milnacipran 200 group, and 6 (14.6%) in the fluvoxamine group ($\chi^2 = 3.74$, df = 2, p = NS). The reasons and dates of dropout are presented in Table 2.

Efficacy

MADS. The changes over time on the MADS in the 3 groups are displayed in Fig. 1. No significant differences were present: $F(2,105) = 0.08$, P = NS. Moreover, the analysis of individual items of the MADS did not reveal any significant difference among the treatment groups.

The percentages of treatment responders, as defined by an improvement of at least 50% from baseline score were respectively 22.0% in the milnacipran 300–150 group, 23.3% in the milnacipran 200 group, and 20.0% in the fluvoxamine group at day 9; respectively 41.5%, 45.2%, and 24.3% at day 14; and respectively 75.0%, 61.0%, and 60.0% at day 28, without significant differences among the 3 groups, despite a somewhat higher rate of responders after 2 weeks in both milnacipran groups and a somewhat higher rate of responders after 4 weeks in the milnacipran 300–150 group.

Hamilton depression scale. The changes over time on the Hamilton depression scale in the 3 treatment groups are presented in Fig. 2. No significant differences were present: $F(2,105) = 0.08$, P = NS. Moreover, changes over time in individual item scores did not reveal any difference among the 3 groups.

The percentages of treatment responders, as defined by an improvement of at least 50% from initial score, were respectively 24.4% in the milnacipran 300–150 group, 18.6% in the milnacipran 200 group, and 22.5% in the fluvoxamine group at day 9; respectively, 43.9%, 33.3%, and 27.0% at day 14; and respectively 75.0%, 58.5%, and 60.0% at day 28, without significant differences among the treatment groups, despite somewhat better results after 2 and 4 weeks in the milnacipran 300–150 group.

CGI. The changes over time on the 3 CGI scores, related to the severity of illness, the global improvement, and the efficacy index, did not exhibit significant differences among the 3 treatment groups: respectively, $F(2,105) = 0.24$, 0.00, and 0.72, P = NS.

Side-effects

The comparison of the frequency of side-effects in the 3 treatment groups is presented in Table 3. Excitement-nervousness and akathisia were more fre-

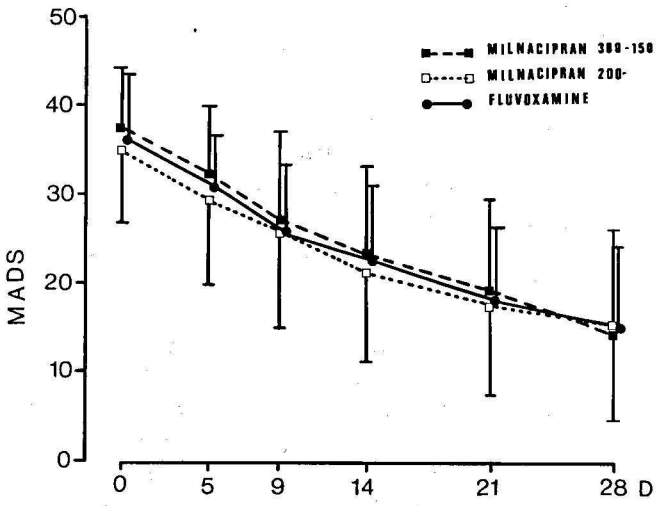

Fig. 1. Changes over time in mean scores (± SD) on the MADS among patients treated by milnacipran 300 mg/d during 2 weeks and 150 mg/d during 2 weeks, milnacipran 200 mg/d, or fluvoxamine 200 mg/d.

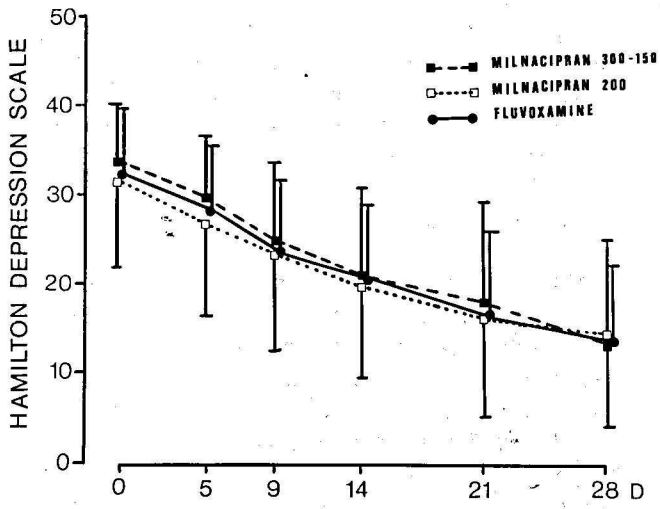

Fig. 2. Changes over time in mean scores (± SD) on the Hamilton depression scale among patients treated by milnacipran 300 mg/d during 2 weeks and 150 mg/d during 2 weeks, milnacipran 200 mg/d, or fluvoxamine 200 mg/d.

quently reported with fluvoxamine.

Pulse rate tended to increase slightly in the milnacipran 300–150 group (from 83.3 ± 11.1 to 86.5 ± 11.2), remained rather stable in the milnacipran 200 group (from 85.0 ± 13.5 to 86.1 ± 9.2) and decreased in the fluvoxamine 200 group (from 84.6 ± 14.9 to 77.9 ± 11.1), responsible for significant differences among the 3 groups ($P = 0.001$). Blood pressure did not exhibit significant changes during the study and EKGs did not reveal significant alterations, except in a female patient, aged 65, who exhibited a few ventricular extrasystoles with milnacipran 300 associated with increasing anxiety.

Mean weight decreased 0.65 kg in the milnacipran 300–150 group, 0.07 kg in the milnacipran 200 group and increased 0.33 kg in the fluvoxamine group, without significant differences among the 3 groups.

Laboratory tests revealed only one case of treatment-related pathological increase in hepatic enzymes (γ-glutamyl-transferase from 22 to 117 UI/l, serum glutamic oxaloacetic transaminase from 23 to 126 UI/l and serum glutamic pyruvate transaminase from 22 to 211 UI/l) in the milnacipran 300–150 group, which rapidly normalized at the end of the treatment period.

Associated anxiolytic and hypnotic benzodiazepines

The mean daily intake of lorazepam did not significantly differ among the 3 groups in the beginning as well as at the end of the treatment: respectively 4.6 and 5.0 mg in the milnacipran 300–150 group, 4.6 and 4.9 mg in the milnacipran 200 group, and 4.6 and 5.2 mg in the fluvoxamine group. The conclusion was similar for the associated intake of nitrazepam: 4.8 and 4.8 mg in the milnacipran 300–150 group, 5.3 and 5.3 mg in the milnacipran 200 group, and 5.2 and 5.4 mg in the fluvoxamine group.

Discussion

The results of the present study do not support the hypothesis that a loading dose of milnacipran can shorten the onset of its clinical efficacy. Indeed, the only parameters where milnacipran 300–150 appear to be somewhat more rapid than the other two groups are the number of treatment responders on the MADS after 4 weeks of treatment (15% more) and on the Hamilton depression scale after 2 and 4 weeks of treatment (11 and 17% more). These differences however do not reach the level of significance.

These negative results could be explained in several ways. First, the loading dose of milnacipran (300 instead of 200 mg/d) may not have been selected high enough, for reasons of unknown tolerance, to be able to differentiate the clinical changes over time. A loading dose of 400 or even 600 mg/d could be tested in the future if data accumulate on the lack of toxicity of such high doses. Second, the delayed onset of antidepressant therapy can be independent from the doses used. We previously demonstrated however that in comparison with amitriptyline the doubling of milnacipran daily dose from 50 to 100 mg/d and further from 100 to 200 mg/d improved the clinical efficacy and shortened the clinical onset (Ansseau et al., 1989a,b; von Frenckell et al., 1990). Taken together, these data suggest that the clinical onset can be shortened with increasing dose until a minimal duration which cannot be further shortened with further increase. This minimal latency could depend on biochemical factors, such as the time necessary to downregulate postsynaptic β-receptors (Bannerjee et al., 1977; Sulser, 1979). It should be noted however, that milnacipran is one of the very few antidepressant compounds which do not induce a down-regulation of β-receptors in animals (Assie et al., 1988). Therefore, caution should be warranted in assuming that down-regulation of beta receptors represents the common final pathway for all clinically active antidepressant agents.

Interestingly, this study clearly shows a lack of apparent dose–response relationship in the two dose regimens of milnacipran tested over the first 2-week period, suggesting that the lower dose is more appropriate.

Several limitations in the design of the study deserve comments. First, the lack of a placebo-treated group makes it necessary to interpret very cautiously all data concerning efficacy. Moreover, the number of patients included in each treatment cell (about 40), even if corresponding to international standards (Angst et al., 1989), could have been too low to demonstrate subtle differences in efficacy. Indeed, many studies containing 40 patients per group failed to find a difference between imipramine and placebo so that a no difference result does not necessarily imply efficacy (Rudorfer and Potter, 1989). The antidepressant efficacy of milnacipran was however previously established in a placebo-controlled study by Macher et al. (1989) showing significant superiority of milnacipran 100 mg/d from the second week of treatment in all rating scales (Hamilton depression scale, MADS, Widlocher's retardation scale) in 2 parallel groups of 29 major depressive inpatients. Moreover, in a previous study, we found significant

superiority of both milnacipran 100 mg/d and amitriptyline 150 mg/d over milnacipran 50 mg/d in 3 parallel groups of 40 major depressive inpatients (Ansseau et al., 1989a). Two other studies showed a lack of significant differences in antidepressant activity between milnacipran 200 mg/d and amitriptyline 150 mg/d (Ansseau et al., 1989b) and between milnacipran 100 mg/d and clomipramine 150 mg/d (Clerc et al., 1990). The number of patients needed in each cell was calculated from tables published by Schwartz (1970) comparing several means among 3 treatment groups for a type 1 error = 1% and a type 2 error = 5%, taking into account that the antidepressant activity of milnacipran and fluvoxamine had been demonstrated in series of 50 or less (Macher et al., 1989; Benfield and Ward, 1986).

The choice of fluvoxamine as reference antidepressant needs to be justified. Indeed, standard tricyclics, such as amitriptyline and imipramine are generally considered as the best reference antidepressants since their efficacy has been well established (Angst et al., 1989). In the present study, all drugs had to be administered from the first day at their full daily dose, what was impossible with classical tricyclics due to their high level of side-effects, particularly of anticholinergic and sedative types. As an example, in our previous studies with amitriptyline 150 mg/d as reference antidepressant, the dose had to be progressively increased over a 5-day period (Ansseau et al., 1989a, 1989b). The antidepressant activity of fluvoxamine has been demonstrated in several placebo-controlled studies (Itil et al., 1983; Amin et al., 1984; Siddiqui et al., 1985; Wakelin and Coleman, 1986; Wakelin, 1988) as well as in a large number of comparisons to standard tricyclics (review in Benfield and Ward, 1986). Moreover, more comparative data involving 'second generation' antidepressants are clearly needed.

The associated intake of anxiolytic and hypnotic benzodiazepines could also represent a confounding factor in the precise detection of clinical improvement. Benzodiazepines are frequently associated with antidepressants among depressive inpatients, and were permitted so as not to modify the habits of some clinicians. It should be remembered, however, that benzodiazepine therapy was initiated during the washout period in order to exclude depressive patients exhibiting significant improvement with anxiolytics, and this could therefore have contributed to the selection of a more homogeneous group of severely depressed inpatients. Moreover, the clinicians were recommended to maintain stable doses of benzodiazepine throughout the study period in order not to influence the rating of some particular symptoms, such as insomnia and anxiety.

The methodology used in this study seems to us more sensitive in detecting subtle differences between active compounds. First of all, the inclusion of severely depressed inpatients instead of moderately depressed outpatients decreases the rate of placebo effect (Ansseau et al., 1991). In the placebo-controlled study of milnacipran by Macher et al. (1989), melancholic inpatients in the placebo group improved by only 8% on the MADS over a 4-week treatment period. All patients included in our study fulfilled RDC criteria for endogenous depression and exhibited very high initial scores of illness severity, despite the use of anxiolytic and hypnotic benzodiazepines, which probably reduced the scores related to anxiety and insomnia. Indeed, in a previous study using a similar methodology, we were able to statistically differentiate two different doses of milnacipran (50 and 100 mg/d) (Ansseau et al., 1989a, 1989b).

Our study demonstrates that milnacipran can be used from the first day of treatment at a dose well above the standard regimen with limited side-effects. Indeed, the rate of side-effects did not differ between milnacipran 200 and 300 mg/d and was lower than with fluvoxamine for two of them: excitement-nervousness and akathisia. In our previous studies (Ansseau et al., 1989a, 1989b), milnacipran was always initiated according to an ascending dose over a 5-day period because the comparison drug, amitriptyline, could not be initiated at its full daily dose (150 mg) due to its anticholinergic and sedative side-effects. With this regard, milnacipran probably represents the first 'second generation' antidepressant with a demonstrated possibility to be administered in doses above the range of active dose from the initiation of the treatment (Feighner, 1986; Rudorfer and Potter, 1989). Our study confirms a previous case report on the use of milnacipran 300 mg/d in obsessive-compulsive disorder where the treatment was also initiated at that same dose (Papart and Ansseau, 1990).

In conclusion, whereas this study does not confirm the clinical usefulness of a loading dose of a 'second generation' antidepressant, such as milnacipran, in the shortening of its therapeutical onset, it confirms the excellent tolerance of the drug.

Acknowledgements

The authors would like to thank Drs. M. Evens, S. Koch-Bourdouxhe, P. Kremer, A. Lecoq, P. Papart who participated in the study, M. von Frenckell-Spiertz, who coordinated the data collection, and C. Gayetot for her secretarial assistance.

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