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Controlled comparison of two doses of milnacipran (F 2207) and amitriptyline in major depressive inpatients

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Abstract. A multicenter study compared the antidepressant efficacy and the tolerance of two doses of milnacipran (50 mg and 100 mg/day) and amitriptyline (150 mg/day) in three parallel groups of 45 major depressive inpatients defined by Research Diagnostic Criteria. After a wash-out period of 4–7 days on placebo with lorazepam and/or nitrazepam if necessary, patients were randomly assigned to a daily dose of milnacipran 50 mg, milnacipran 100 mg or amitriptyline 150 mg reached on the 5th day and then stable over a 4-week period, with weekly assessments by means of the Montgomery and Asberg depression scale, the Hamilton depression scale, the Clinical Global Impressions (CGI) and the Target Emergent Signs and Symptoms. Results showed significant superiority of both milnacipran 100 mg/day and amitriptyline over milnacipran 50 mg/day at the end of the treatment period. However, amitriptyline induced a nonsignificant trend toward more rapid improvement after 2 weeks of treatment, mainly based on items related to insomnia, supporting more sedative properties of amitriptyline as compared to milnacipran. Anticholinergic side-effects were significantly lower with milnacipran than with amitriptyline, explaining why milnacipran 100 mg exhibited at the end of the treatment period, a nonsignificantly better efficacy index on the CGI. Moreover, in contrast to milnacipran, amitriptyline was responsible for a significant decrease in blood pressure and a significant weight gain.

Key words: Milnacipran – Midalcipran – F 2207 – Antidepressant –Amitriptyline – Major depression

Milnacipran (l-phenyl-l-diethyl-amino-carbonyl-2-aminomethylcyclopropane hydrochloride) previously midalcipran or F 2207 (Fig. 1) is a new potential antidepressant selected for its equipotent inhibition of noradrenaline and serotonin uptake and its lack of effect at any postsynaptic receptor (Moret et al. 1985). In behavioural tests based on interaction with the noradrenergic system, such as antagonism of tetrabenazine-induced ptosis, potentiation of yohimbine-induced toxicity, and antagonism of apomorphine or oxotremorine-induced hypothermia, milnacipran is extremely active (Stenger et al. 1987). Similarly, milnacipran shows potent activity on serotonergic tests, such as enhancement of the behavioural changes induced by *l*-tryptophan and antagonism of *p*-chloramphetamine-induced hyperthermia (Stenger et al. 1987). Milnacipran is also effective in the "behavioural despair" animal model of depression but is devoid of effect in animal tests of anticholinergic activity (Stenger et al. 1987). Despite its structural resemblence to tranylcypromine, milnacipran has no effect on monoamine oxidase activity (Moret et al. 1985). This biochemical and pharmacological profile suggested that milnacipran might be a potent antidepressant devoid of anticholinergic side-effects. Indeed, the activity on both the noradrenergic and serotonergic systems has recently been suggested to improve the antidepressant action (Van Praag 1984). An open pilot study on 27 major depressed patients has shown that milnacipran (100 mg daily) had a significant antidepressant effect within 7 days; in addition, the drug was well tolerated without anticholinergic side-effects (Serre et al. 1986).

Therefore, the purpose of the present study was to confirm the antidepressant efficacy and the good tolerance of milnacipran at two daily doses (50 and 100 mg) as compared to a standard antidepressant, amitriptyline, among major depressive inpatients.

Subjects and methods

Design of the study. The study was performed between July 1986 and July 1987 in ten Belgian centers used to collaborate and exhibiting good reliability in clinical rating (see affiliations). The trial used a double-blind design with three parallel groups of patients randomly assigned to milnaci-

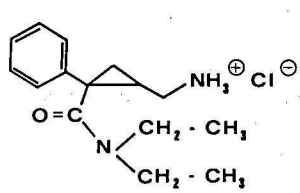

Fig. 1. Structural formula of milnacipran (F 2207)

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Table 1. Frequency of RDC subtypes of major depression

	Milnacipran 50 group $n=42$	Milnacipran 100 group $n=44$	Amitriptyline 150 group $n=45$
Primary/secondary	38/4	39/5	40/5
Recurrent	25	28	33
Psychotic	6	5	5
Incapacitating	34	32	39
Endogenous	39	37	39
Agitated	9	10	13
Retarded	29	36	32
Situational	11	16	16
Predominant mood			
mainly depressed	31	27	31
mainly apathetic	9	15	9
other	2	2	5

pran 50 mg/day, milnacipran 100 mg/day, or amitriptyline 150 mg/day. The daily dose was progressively increased from day 1 to day 5: 12.5 mg, 25 mg, 25 mg, 50 mg, and 50 mg in the milnacipran 50 group; 25 mg, 50 mg, 75 mg, 75 mg, and 100 mg in the milnacipran 100 group; and 50 mg, 75 mg, 100 mg, 125 mg, and 150 mg in the amitriptyline 150 group. The treatment was administered in two daily intakes, morning and evening. All drugs were administered by nurses, who were instructed to pay special attention that the patients swallow their tablets in front of them. The active period was preceded by a wash-out period of 4–7 days on placebo and lorazepam (up to 10 mg/day) and nitrazepam (up to 5 mg/day) if needed. These associated drugs could be maintained during the treatment period if necessary. The duration of the study was 4 weeks, with weekly assessments.

Subjects. A total of 144 inpatients were included in the study, 13 of whom were not included in the statistical analysis for early drop-out (before day 14) or for nonrespect of the protocol: 4 in the milnacipran 100 group, 5 in the milnacipran 50 group, and 4 in the amitriptyline 150 group. Therefore, the milnacipran 50 group comprised 44 patients, the milnacipran 100 group 42 patients and the amitriptyline group, 45 patients. Patients were 45 males and 86 females, aged from 20 to 70 years, with a mean age (SD) of 48.6 (10.9) years. All subjects were depressive inpatients who fulfilled Research Diagnostic Criteria (RDC) for a definite major depressive disorder (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 4 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 59 with a mean (SD) of 37.1 (7.7) on the MADS and from 13 to 56 with a mean (SD) of 33.0 (8.5) on the Hamilton depression scale. Patients presenting any evidence of contra-indication for a tricyclic antidepressant or serious or uncontrolled medical illness were excluded from the study. The characteristics of the patients according to RDC subtypes of major depression are presented in Table 1.

All patients should remain hospitalized for at least the first 2 weeks of treatment. Finally, all patients were fully informed of the purpose of the study and gave their consent.

Assessments. Weekly assessments were performed by means of the MADS, the 24-item Hamilton depression scale (Hamilton 1960; Guy 1976), the CGI, and the Target Emergent Signs and Symptoms (TESS) (Guy 1976). Pulse and blood pressure in the supine and standing positions were measured weekly. An elektrocardiogram (ECG) was performed before treatment and 2 weeks later whereas laboratory tests, including hepatic and renal balance-sheets, were performed before treatment and at the end of the treatment period. Finally, a global evaluation of the therapeutical outcome, the level of satisfaction, and the desire to continue the same treatment was performed after completion of the study period.

Data analysis. First of all, the homogeneity of the three treatment groups was controlled. No significant differences were present related to age, weight, height, gender and civil status distribution, the three scores of the Raskin and Covi scale, the scores on the MADS and the Hamilton scale, the frequency of RDC subtypes of major depression, the previous psychotropic treatments, and the personal and family psychiatric history. The homogeneity among the ten centers in the baseline severity of depressive symptomatology, as measured by the Raskin scale, the MADS, and the Hamilton scale was tested by an analysis of variance (ANOVA). Since all scales exhibited significant differences between centers [$F(9,101)=7.4$, $P=0.0001$ for the Raskin scale, $F(9,101)=11.5$, $P=0.0001$ for the MADS, and $F(9,101)=9.8$, $P=0.0001$ for the Hamilton scale], the changes over time in depressive symptomatology were analyzed in percentage of improvement related to the baseline scores.

Baseline data of the three treatment groups were compared by an analysis of variance (ANOVA) or by a Chi square statistics, eventually corrected by the Yates test for small samples. Then, all changes over time in ratings were assessed by an ANOVA with repeated measures. A first analysis was performed from day 0 to day 14 in order to keep the whole sample without missing data. A second analysis was performed from day 0 to day 28 for all cases having been treated for the whole period. A last analysis was then performed from day 0 to day 28 with reporting of the endpoint scores for subsequent evaluations of patients who did not complete the 4-week protocol, but since the conclusions were similar they will not be reported herein. All ANOVA with repeated measures were followed by time by time ANOVA associated with Bonferroni tests in order to complete the comparison among groups at intermediate times. All statistical procedures used a SAS package.

Results

Drop-outs

A total of 22 patients (17%) left the study between day 14 and day 28 for lack of efficacy or side-effects: 5 (11%) in the milnacipran 100 group, 10 (24%) in the milnacipran 50 group, and 7 (16%) in the amitriptyline group ($X^2=2.5$, $df=2$, $P=$NS).

Efficacy

MADS. The changes over time on the MADS in the three groups are displayed in Fig. 2. During the first 2 weeks

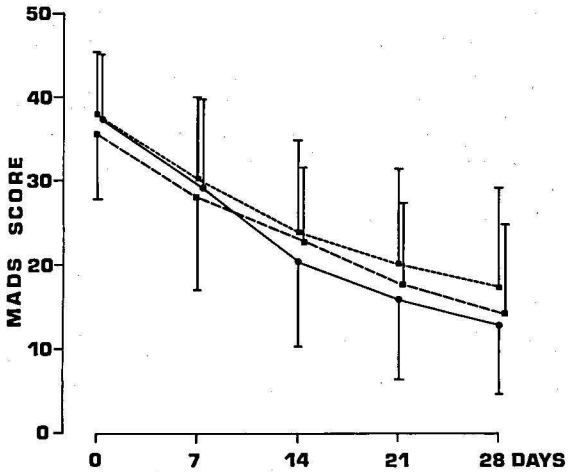

Fig. 2. Changes over time in mean scores (±SD) on the MADS among patients treated by milnacipran 100 mg/day, milnacipran 50 mg/day, or amitriptyline 150 mg/day. ■---■ Milnacipran 100; ■---■ Milnacipran 50; ●—● Amitriptyline

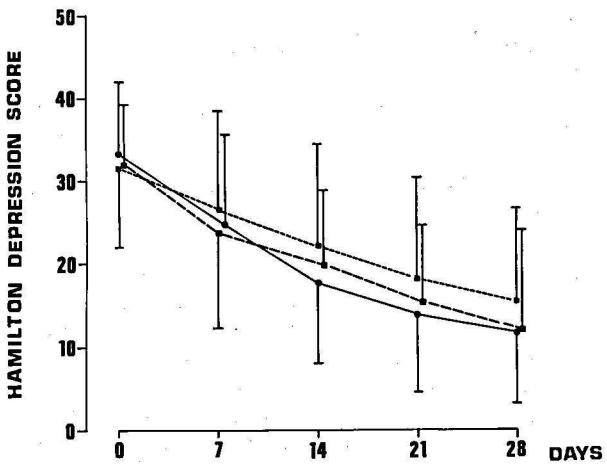

Fig. 3. Changes over time in mean scores (±SD) on the Hamilton depression scale among patients treated by milnacipran 100 mg/day, milnacipran 50 mg/day, or amitriptyline 150 mg/day. ■---■ Milnacipran 100; ■---■ Milnacipran 50; ●—● Amitriptyline

of treatment, amitriptyline exhibited a significant superiority over the two doses of milnacipran [$F(2,128)=3.7$, $P=0.03$], with Bonferroni tests exhibiting a nonsignificant trend toward differences at day 14 ($P=0.08$). The analysis over the 4-week period exhibited a trend toward significant differences in the evolution of the three treatment groups [$F(6,318)=1.9$, $P=0.08$]. The difference previously noted at day 14 was still present ($P=0.09$, trend) but tended to disappear at day 21 and at day 28, where the results of milnacipran 100 mg were similar to those of amitriptyline. The Bonferroni tests yielded no significant results.

Hamilton depression scale. The changes over time on the 24-item Hamilton depression scale in the three treatment groups are displayed in Fig. 3. Initial and final corresponding scores (SD) on the 17-item scale were respectively 24.4 (5.3) and 9.2 (6.7) in the milnacipran 100 mg group, 25.1 (7.0) and 11.4 (7.9) in the milnacipran 50 group, and 24.8 (6.1) and 8.1 (5.7) in the amitriptyline group. During the

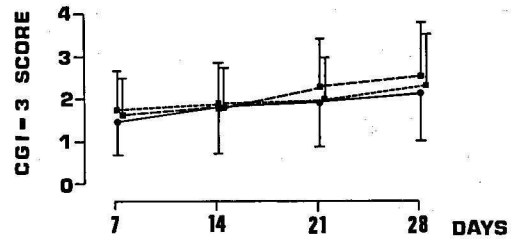

Fig. 4. Changes over time in mean score (±SD) on the CGI related to efficacy index among patients treated by milnacipran 100 mg/day, milnacipran 50 mg/day, or amitriptyline 150 mg/day. ■---■ Milnacipran 100; ■---■ Milnacipran 50; ●—● Amitriptyline

first 2 weeks of treatment, amitriptyline exhibited a significant superiority over the two doses of milnacipran [$F(2,128)=3.7$, $P=0.03$], with Bonferroni tests exhibiting a nonsignificant trend toward differences at day 14 ($P=0.09$). The analysis over the entire 4-week period did not exhibit any significant differences in the evolution of the three treatment groups [$F(6,318)=1.5$, $P=$NS]. Again, the difference previously noted at day 14 was still present [$F(2,106)=2.7$, $P=0.08$, trend] but tended to disappear at day 21 and at day 28, where the results of milnacipran 100 mg were similar to those of amitriptyline.

The comparison of the evolution of the six factor scores of the Hamilton scale defined in Guy (1976) revealed significant superiority of amitriptyline over milnacipran 100 and 50 mg at day 14 for anxiety/somatization [$F(2,124)=4.82$, $P=0.01$] and at days 14, 21, and 28 for sleep disturbances [$F(2,101)=5.89$, $P=0.004$]. The evolution of the other factors (weight, cognitive disturbance, diurnal variation, and retardation) did not exhibit significant differences among the three treatment groups.

CGI. During the first 2 weeks of treatment, amitriptyline improved the CGI-1 scores, related to severity of illness, significantly more than the two doses of milnacipran [$F(2,128)=4.5$, $P=0.02$]. The analysis over the entire 4-week period did not reveal any significant difference in the evolution of the three treatment groups.

On the CGI-2, related to the global improvement, amitriptyline was also superior to the two doses of milnacipran during the first 2 weeks of treatment [$F(2,128)=3.7$, $P=0.03$]. The analysis over the entire 4-week period exhibited only a trend toward a significantly different evolution among the three treatment groups [$F(6,318)=1.9$, $P=0.08$], without any differences on the Bonferroni tests.

During the first 2 weeks of treatment as well as the entire 4-week period, no difference in the changes over time in the CGI-3 scores, related to the efficacy index, existed among the three groups [respectively [$F(2,128)=0.4$, $P=$NS and $F(6,318)=1.3$, $P=$NS], despite a better efficacy index at the end of treatment with milnacipran 100 mg (Fig. 4).

Global assessments. The distribution of global rating of the therapeutical result at the end of the treatment did not present any difference among the three groups: 20 excellent and good, 9 moderate and doubtful, and 13 mild or bad with milnacipran 50 mg; 26 excellent or good, 10 moderate or doubtful, and 8 mild or bad with milnacipran 100 mg; and 28 excellent or good, 9 moderate or doubtful and 6 mild or bad with amitriptyline ($X^2=4.4$, $df=4$, $P=$NS).

The global assessment of the therapeutical outcome exhibited a statistically significant different distribution among the 3 groups ($X^2=12.4$, $df=6$, $P=0.05$). With amitriptyline, the clinician was very satisfied in 30% of the cases, satisfied in 47%, undecided in 5%, and not satisfied in 19%. In contrast, the opinion of the investigator about milnacipran exhibited a more bimodal distribution: for milnacipran 100, 39% of very satisfactory, 23% of satisfactory, 16% of undecided, and 23% of not satisfactory; with milnacipran 50, 31% of very satisfactory, 19% of satisfactory, 14% of undecided, and 36% of not satisfactory.

The global rating of the therapeutical outcome by the patients themselves followed a distribution identical to that of the psychiatrist ($X^2=10.7$, $df=6$, $P=0.09$, trend). No significant differences existed among the three groups with regard to the desire to continue the same treatment, despite a somewhat lower frequency with milnacipran 50 mg (40%) compared to milnacipran 100 mg (61%) and amitriptyline (53%).

Side-effects

With regard to side-effects, drowsiness was significantly more frequent at day 14 with amitriptyline than with milnacipran 100 mg (24% versus 5%, $z=2.7$, $P=0.01$). Dryness of the mouth was also much more often reported with amitriptyline than with milnacipran 100 or 50 mg: at day 14, by respectively 71%, 30%, and 24% of the patients, indicating higher frequency with amitriptyline than with milnacipran 100 ($z=3.9$, $P=0.0001$) as well as 50 mg ($z=4.4$, $P=0.0001$); and at day 28, respectively by 74%, 28%, and 16% of the patients, indicating higher frequency with amitriptyline than with milnacipran 100 ($z=4.0$, $P=0.0001$) and 50 mg ($z=4.8$, $P=0.0001$). Constipation was somewhat more frequently reported with amitriptyline than with milnacipran 100 or 50 mg (at day 14: 44%, 30%, and 29%) but without statistically significant differences.

While the supine systolic blood pressure showed a decrease for the whole sample between day 0 and day 7 [$F(4,312)=2.9$, $P=0.03$] without significant differences among groups [$F(8,312)=1.1$, $P=0.3$, p = NS], the diastolic blood pressure did not exhibit any significant change over time. The standing systolic blood pressure exhibited a significant decrease between day 0 and day 28 for the whole sample [$F(4,308)=2.9$, $P=0.03$] which was especially present in the amitriptyline group [$F(8,308)=1.7$, $P=0.10$, trend]. The Bonferroni tests showed that at day 21, this blood pressure was significantly lower with amitriptyline than with milnacipran 100 mg ($P<0.05$). The same conclusion was applicable for the diastolic blood pressure.

With regard to weight, amitriptyline induced a mean increase of 2.1 kg over the 4-week period, which was statistically very significant ($t=-3.7$, $P=0.0006$) while milnacipran 50 mg and 100 mg did not induce any significant changes (respectively -0.7 kg, $t=1.2$ and -0.2 kg, $t=1.6$).

Finally, no significant alterations in the ECG's and in the laboratory tests were noted in any of the treatment groups.

Associated anxiolytic and hypnotic benzodiazepines

The associated intake of anxiolytic and hypnotic benzodiazepines did not exhibit significant differences among the three treatment groups. The initial mean dose (SD) of lorazepam was 2.8 mg (2.9) in the milnacipran 100 group, 3.7 mg (3.9) in the milnacipran 50 group, and 3.0 mg (3.5) in the amitriptyline group and after 4 weeks, respectively 3.1 mg (3.9), 2.7 mg (3.5), and 2.8 mg (3.4). For nitrazepam, the initial mean dose (SD) was 2.0 mg (2.7) in the milnacipran 100 group, 3.0 mg (2.9) in the milnacipran 50 group, and 2.6 mg (2.7) in the amitriptyline group and after 4 weeks, respectively 2.8 mg (3.2), 3.0 mg (2.8), and 1.8 mg (2.6).

Discussion

The results of the present study show significant superiority of amitriptyline 150 mg and milnacipran 100 mg over milnacipran 50 mg after 4 weeks of treatment. However, the latency of the clinical improvement is somewhat longer with milnacipran than with amitriptyline with more clinical improvement with amitriptyline at the end of the first 2 weeks of therapy.

The differences favoring amitriptyline after 2 weeks probably do not reflect true antidepressant superiority but the more sedative profile of amitriptyline. Indeed, the individual analysis of the changes over time in the 24 items of the Hamilton depression scale reveals only significant differences or trend toward significant differences for initial insomnia [$F(2,128)=3.3$, $P=0.05$], middle insomnia [$F(2,128)=3.6$, $P=0.03$], and terminal insomnia [$F(2,128)=3.1$, $P=0.05$] after 2 weeks of treatment. The analysis of the Hamilton depression scores without these three items related to insomnia still shows a trend toward significant differences among the three groups at day 14 [$F(1,128)=2.8$, $P=0.07$] but a lack of significant differences at the end of the treatment period. These conclusions are confirmed by the item analysis of the MADS, which shows very significant differences favoring amitriptyline at day 14 for sleep loss [$F(2,128)=7.5$, $P=0.0008$] but also significant differences among the three groups for the item "inner tension" [$F(4,256)=3.4$, $P=0.01$]. It should be noted that the scores on the "inner tension" item also diminish with milnacipran, but less than with amitriptyline, which can be related to a more stimulating activity of milnacipran or to the well-known sedative effects of amitriptyline (Enelow 1975). This interpretation is supported by the lower mean dose of nitrazepam used in the amitriptyline group compared to the milnacipran 100 and 50 groups, particularly at the end of the treatment period, even if statistically non-significant (respectively, 1.8 mg$\pm$2.6; 2.8 mg$\pm$3.2; and 3.0 mg$\pm$2.8); however, no difference is noted in the associated intake of lorazepam which remained very similar in the three treatment groups. The low rate of sedative side-effects with milnacipran may result from the lack of affinity of the compound for alpha-1-noradrenergic and histamine-H-1 receptors, which contrasts to amitriptyline (Moret et al. 1985).

It should also be noted that the initial progressive increase in the treatment doses over a 5-day period was needed in order to limit the anticholinergic and sedative side-effects of amitriptyline; milnacipran could have been administered at the active dose from the first day with a consequent shortening of the clinical latency.

Caution should be maintained in concluding similar efficacy of milnacipran 100 and amitriptyline 150 from a lack of significant differences, particularly in the absence of a placebo group. However, the dose-response relationship be-

tween milnacipran 50 and 100 mg supports the antidepressant efficacy of milnacipran 100 mg and suggests that the risk of a type II error is limited. At any rate, placebo-controlled studies as well as other trials including large number of depressive patients need to be performed in order to confirm the antidepressant efficacy of milnacipran.

Milnacipran was responsible for significantly less anticholinergic side-effects (dryness of the mouth) than amitriptyline. These results confirm the lack of affinity of milnacipran for muscarinic receptors (Moret et al. 1985) as well as its lack of activity in animal tests showing an interaction with the cholinergic system (Stenger et al. 1987). Milnacipran did not differ from amitriptyline with regard to digestive side-effects. This is particularly interesting, since most recent antidepressants, such as viloxazine, trazodone, fluvoxamine, or fluoxetine, induce less anticholinergic side-effects than standard tricyclics but more digestive side-effects, such as nausea or vomiting (Feighner 1986). On the other hand, patients on milnacipran did not gain weight, which contrasts with the 2.1 kg mean increase induced by amitriptyline over a 4-week period. Milnacipran shares this advantage, which may relate to its lack of effects on histaminic receptors, with other recent antidepressants, such as the selective serotonin reuptake inhibitors fluvoxamine and fluoxetine (Feighner 1986). Moreover, milnacipran also induced less hypotension than amitriptyline. This overall lower rate of side-effects may explain why milnacipran 100 mg obtains better scores than amitriptyline on the therapeutic index of the CGI, which takes into account both efficacy and side-effects of the treatments.

The global assessement of the therapeutical outcome exhibits a different distribution among the three treatment groups. While amitriptyline shows a unimodal distribution, milnacipran shows a bimodal distribution with poorer or better results. This type of "all or nothing" response has frequently been suggested for recent antidepressants and has been explained by their biochemical specificity (serotonergic or noradrenergic). However, milnacipran possesses rather equipotent activity on the serotonergic and noradrenergic systems, suggesting that this hypothesis may not be applicable.

The dose-response relationship between milnacipran 50 and 100 mg may suggest that a higher dose of milnacipran could improve its antidepressant efficacy, particularly in view of its low rate of side-effects. The selection of the 100 mg daily dose for milnacipran was essentially based on an open pilot study in 27 major depressive inpatients which showed excellent or good results in 68% of the patients (Serre et al. 1986). In this study, the initial dose of milnacipran was 100 mg daily, and could be doubled after 2 weeks. Ten patients were then treated with 200 mg/day while 17 patients remained at the 100 mg daily dose. The comparison of outcome between these two subgroups did not appear to confer special benefit. However, this conclusion may be criticized. Obviously, the patients who requested 200 mg daily were those unresponsive to the 100 mg dose and the similar outcome in the 100 mg and the 200 mg groups might be an argument suggesting that some depressed patients may benefit from higher doses.

This study shows statistically significant differences in antidepressant efficacy between different doses of an active compound. Such differences are rather rare in the literature and may depend on the methodology used. Studies with inpatients presenting with a high level of illness severity are more sensitive than studies with outpatients. For example, clinical studies comparing alprazolam with standard antidepressants among major depressive outpatients did not show significant differences (review in Ansseau et al. 1984 and in Warner et al. 1988) while the two studies using a small number of severely depressed inpatients showed better efficacy of amitriptyline over alprazolam (Lenox et al. 1984; Rush et al. 1985). Depressed inpatients are more severely depressed and less responsive to placebo. In our study, 88% of the patients exhibited endogenous features, as defined by RDC. Moreover, the initial scores of illness severity were very high: 33 on the Hamilton scale and 37 on the MADS, despite the use of anxiolytic (a mean daily dose of 3.2 mg of lorazepam) and hypnotic (a mean dose of 2.5 mg of nitrazepam) benzodiazepines, which probably reduced the scores related to anxiety and insomnia.

In conclusion, this study shows a better antidepressant efficacy of milnacipran 100 mg compared with milnacipran 50 mg. However, the fact that a higher dose of milnacipran might improve the therapeutical results in such type of severely depressed inpatients deserves to be tested in another study.

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References

Ansseau M, Ansoms C, Beckers G, Bogaert M, Botte L, De Buck R, Diricq S, Dumortier A, Jansegers E, Owieczka J, Stellamans G (1984) Double-blind clinical study comparing alprazolam and doxepin in primary unipolar depression. J Affective Disord 7:287–296

Covi L, Lipman R, McNair DM, Czerlinski T (1979) Symptomatic volunteers in multicenter drug trials. Prog Neuropsychopharmacol 3:521–533

Enelow AJ (1975) Amitriptyline in the management of depression: an overview. In: Amitriptyline in the management of depression. Merck Sharp and Dohme, West Point, PA, pp 139–161

Feighner JP (1986) The new generation of antidepressants. In: Rush AJ, Altschuler KZ (eds) Depression: basic mechanisms, diagnosis, and treatment. Guildford Press, New York, pp 205–225

Guy W (ed) (1976) ECDEU Assessment manual for psychopharmacology (revised). National Institute of Mental Health, Psychopharmacology Research Branch, Rockville, MD

Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 12:56–62

Lenox RH, Shipley JE, Peyser JM, Williams JM, Weaver LA (1984) Double-blind comparison of alprazolam versus imipramine in the inpatient treatment of major depressive illness. Psychopharmacol Bull 20 (1):79–82

Montgomery A, Asberg M (1979) A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389

Moret C, Charveron M, Finberg JPM, Couzinier JP, Briley M (1985) Biochemical profile of midalcipran (F 2207), l-phenyl-l-diethyl-aminocarbonyl-2-aminomethyl-cyclopropane (Z) hydrochloride, a potential fourth generation antidepressant drug. Neuropharmacology 24:1211–1219

Raskin A, Schulterbrandt J, Reatig N, Rice CE (1967) Factors of psychopathology in interview, word behavior and self-report ratings of hospitalized depressions. J Consult Psychol 31:270–278

Rush AJ, Erman MK, Schlesser MA, Roffwarg HP (1985) Alpra-

zolam vs amitriptyline in depression with reduced REM latencies. Arch Gen Psychiatry 42:1154–1159
Serre C, Clerc G, Escande M, Feline A, Ginestet D, Tignol J, Van Amerongen P (1986) An early clinical trial of midalcipran, a potential fourth generation antidepressant. Curr Ther Res 39:156–164
Spitzer RL, Endicott J, Robins E (1978) Research Diagnostic Criteria: rationale and reliability. Arch Gen Psychiatry 34:773–778
Stenger A, Couziner JP, Briley M (1987) Psychopharmacology of midalcipran, l-phenyl-l-diethyl-amino-carbonyl-2-aminomethylcyclopropane hydrochloride (F 2207), a new potential antidepressant. Psychopharmacology 91:147–153
Van Praag HM (1984) Studies in the mechanism of action of serotonin precursors in depression. Psychopharmacol Bull 20:599–602
Warner MD, Peabody CA, Whiteford HA, Hollister LE (1988) Alprazolam as an antidepressant. J Clin Psychiatry 49:148–150

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