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Milnacipran and pindolol: a randomized trial of reduction of antidepressant latency

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Background New, better tolerated and faster treatments for depression are needed. Patients are understandably unhappy with having to wait 3 to 4 weeks for a response to an antidepressant, while experiencing side effects almost immediately. This frequently has an adverse effect on compliance and engagement with treatment.
Aims The primary objective was to assess the activity of pindolol on the onset of antidepressive response of milnacipran. The secondary objective was to assess the number of responders among the patients who received milnacipran and pindolol versus patients who received milnacipran and placebo. The tertiary objective was to evaluate the safety of milnacipran and pindolol versus milnacipran and placebo.
Method Randomized, double-blind, placebo-controlled study over 42 days.
Setting Inner city London community mental health teams.
Participants 80 patients were selected and gave written consent to treatment, 78 were randomized (39 in each group) and evaluated for safety (intention-to-treat, ITT, safety data set), 77 (ITT efficacy data set), and 64 (per protocol, PP, data set) were evaluated for efficacy. The mean age was 31.9 for the pindolol group and 32.3 for the placebo.
Intervention All patients received milnacipran 50 mg twice a day plus either pindolol 2.5 mg (the 'pindolol group') or matching placebo (the 'placebo group') three times a day.
Outcome measures The main efficacy variable was the Montgomery–Åsberg depression rating scale (MADRS) score at days 0, 4, 7, 10, 14, 21, 28, 42 on PP data set in an observation carried (OC) approach. Secondary efficacy variables were clinical global impression (global improvement) and Hamilton depression rating scale (HDRS).
Results Improvement in MADRS total score was greater in the pindolol group than in the placebo group from day 7 ($p = 0.03$). Responder rates in the clinical global impression were 97.2% for the pindolol group and 60.6% for the placebo group. The treatment was well tolerated with the most common side effects being nausea (28.2%; 35.9%), vomiting (7.7%; 23.1%), hot flushes (15.4%; 5.1%) and sweating (12.8%; 12.8%).
Conclusion The milnacipran and pindolol combination is safe, well tolerated and efficacious in major depression, and represents a rational strategy for the possible acceleration or potentiation of antidepressant action.

KEY WORDS — SSRI; milnacipran; pindolol; 5-HT1A receptor; depression; antidepressants; randomized controlled trial

INTRODUCTION

Depression is the fourth most common cause of global burden of disability and is projected to become the second most common cause of disability by 2020 (World Health Organization, 2001).

In the midbrain raphé, 5HT1A receptors are localized chiefly in pre-synaptic arrays, where they form

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somato-dendritic autoreceptors. When the receptor is stimulated, the firing of the 5HT (5-hydroxytryptamine, serotonin) neuron, and the release of 5HT is reduced (Sinton and Fallon, 1988; Blier *et al.*, 1990; Invernizzi *et al.*, 1991; Artigas, 1993; Hoyer, 1991).

The current broad consensus is that the enhancement of 5HT neurotransmission that follows 5HT reuptake blockade is limited by the negative feedback control exerted by activation of 5HT autoreceptors (Bel and Artigas, 1992; Hjorth and Auerbach, 1994). The delay of activity of antidepressants such as selective serotonin reuptake inhibitor (SSRI) drugs has been explained by a negative feedback mechanism involving the presynaptic 5HT1A autoreceptor (Blier *et al.*, 1997) and provided the original theoretical basis of the early clinical combination of an SSRI with a 5HT1A blocking compound to accelerate the onset of action of an antidepressant.

No *pure* inhibitors of 5HT1A are generally available for clinical use in humans, and small-scale open studies in Spain (Artigas *et al.*, 1994; 1996) and Canada (Blier and Bergeron, 1995) intimated that augmentation of the SSRIs with pindolol, a beta-blocker with 5HT1A receptor antagonist activity, could result in symptomatic relief of depression within days rather than weeks (Blier and Montigny, 1994). The effect was noted with fluoxetine and paroxetine and occurred in both drug-naive and treatment-resistant patients when pindolol was added to the current SSRI. There have been numerous open label studies of the combination of sertraline (Dinan and Scott, 1996), nefazodone (Bakish *et al.*, 1997), trazodone (Maes *et al.*, 1996), fluvoxamine (Zanardi *et al.*, 1997) and venlafaxine (Beique *et al.*, 2000; MTI unpublished) with pindolol which have tested the safety of pindolol as an augmenter of antidepressants.

Pindolol is a lipophilic, relatively non-selective beta-1 and beta-2 adrenergic blocker with some intrinsic sympatheticomimetic effects but little or no quinine-like membrane-stabilizing qualities. It has been used in psychiatric patients to treat anxiety (British National Formulary, 2001), but its main use is in the treatment of hypertension. Unlike propranolol, pindolol has not been implicated in causing depression (Rasanen *et al.*, 1999).

Milnacipran is a novel antidepressant, which blocks noradrenaline (NA) and serotonin reuptake at the presynaptic neuron. It is licensed in 33 countries, including France and Japan for the treatment of depression. This dual action is shared by other antidepressants such as venlafaxine and duloxetine.

Animal studies (reviewed by Briley and Montgomery, 1998) indicate that concurrent pindolol and milnacipran administration is followed by an increase in forebrain NA and 5HT neuronal firing.

Our group performed the first double-blind randomized study of a combination of paroxetine and pindolol (Tome *et al.*, 1997b). We showed an accelerated response to the combination in patients without previous treatment with antidepressants.

METHODS

Subjects

The Affective Disorders Clinic of South London and Maudsley Trust at University Hospital Lewisham receives referrals of patients with a preliminary diagnosis of depression from local general practitioners, Accident and Emergency departments, psychiatric and other services in a socially disadvantaged area of inner city London (Lewisham, population 250 000); and secondary and tertiary referrals from elsewhere.

Inpatients or outpatients aged from 18 to 70 years were recruited with a diagnosis of moderate or severe unipolar depression (without psychotic symptoms) defined according to DSM-IV criteria, and who scored at least 18 on the Montgomery–Åsberg depression rating scale (MADRS) (Montgomery and Åsberg, 1979).

Inclusion criteria comprised a history of no more than two recurrent episodes of unipolar depression, with or without melancholia, and without psychotic features. Exclusion criteria included conditions such as asthma, diabetes, cardiopulmonary disease and other significant co-existing factors, which proscribed use of the study medication.

Patients who had required ECT within the previous 3 months and/or had taken an antidepressant in the previous 2 weeks were also excluded from the study, as were patients suffering from mental illnesses such as schizophrenia, psychotic (delusional) disorder or bipolar affective disorder. Written informed consent was obtained in every case and the study was approved by the Local Research Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki and European Good Clinical Practice guidelines.

Socio-demographic characteristics such as the number of children, marital status, number in household; educational level and current employment status were recorded.

Number of patients

Sample size was calculated to show a difference between the two treatment groups with the following hypothesis, based on the results of our previous study

(Tome *et al.*, 1997b). 1. Expected difference between treatment group means of MADRS score during the second week = 6. 2. Standard deviation = 8.6. 3. α (two-sided) = 5%. 4. β = 20%.

Thirty three patients per group were needed. Forty patients per group were included to account for drop-outs and protocol deviations.

Assessments

Patients were assessed on MADRS, Hamilton depression rating scale (HDRS: 17-Items, 1967) and clinical global impression (CGI, a measure of severity of illness: Guy, 1976) at days 0, 4, 7, 10, 14, 21, 28 and 42. CGI severity of the illness was recorded using a 7-point scale ranging from '*Normal, not at all ill*' (score of 1) to '*Amongst the most severely ill patients*' (score of 7).

Treatment

Patients were randomized according to a computer-generated randomization list to receive either milnacipran (50 mg twice daily) plus pindolol (2.5 mg three times daily: the 'pindolol group') or milnacipran (50 mg twice daily) plus placebo to match pindolol (three times daily: the 'placebo group'). At day 42 patients were given the option to continue with milnacipran alone.

The patients in the 6 week study were subsequently switched to open label milnacipran alone and followed up for a further 18 weeks. This extension study aimed to ensure the possibility of access to treatment for any patient that had responded to medication. The results presented here relate to the 6 week period only.

Analysis of results

Except where stated, our results refer to the intent-to-treat (ITT) population, which includes all patients who received at least one dose of randomized treatment. Tests were two-sided, with a p value of less than 0.05 regarded as significant. The primary efficacy variable was change in MADRS total score. Another clinically important variable was response in CGI global improvement, predefined as the proportion of patients who were '*very much*' and '*much*' improved. The change from baseline in MADRS and HDRS score was compared between groups using analysis of variance with terms fitted for treatment group and baseline score.

RESULTS

Eighty-four patients were selected and 78 were randomized. The intent-to-treat (ITT) data set for safety analysis included 78 patients: 39 who received milnacipran + pindolol and 39 who received milnacipran + placebo. One patient had no efficacy evaluation and was excluded from the ITT data set for efficacy analysis (39 milnacipran + pindolol, 38 milnacipran + placebo). The per protocol (PP) data set comprised 64 patients: 35 received milnacipran + pindolol and 29 received milnacipran + placebo.

Of 78 patients randomized, 12 withdrew from the study: 4 receiving milnacipran + pindolol, and 8 receiving milnacipran + placebo. The commonest reasons for withdrawal were adverse events and patient's decision.

Sociodemographic characteristics are shown in Table 1. Demographic characteristics are shown in

Table 1. Sociodemographic characteristics

	Milnacipran + Pindolol $n = 39$	Milnacipran + Placebo $n = 39$
Number of children		
0		
1	19 (48.7%)	21 (53.8%)
2	9 (23.1%)	4 (10.3%)
3	6 (15.4%)	7 (17.9%)
3+	5 (12.8%)	4 (10.3%)
		3 (7.7%)
Marital status		
Married		
Divorced	12 (30.8%)	9 (23.1%)
Single	5 (12.8%)	9 (23.1%)
Widowed	22 (56.4%)	20 (51.3%)
		1 (2.6%)
Daily living		
Alone	9 (23.1%)	12 (31.6%)
With relatives	30 (76.9%)	25 (65.8%)
Educational levels		
Able to read	1 (2.6%)	7 (17.9%)
Primary	5 (13.2%)	9 (23.1%)
Leaving O-level	9 (23.7%)	2 (5.1%)
Left not having A-level	4 (10.5%)	4 (10.3%)
Leaving A-level	2 (5.3%)	2 (5.1%)
Higher education	17 (44.7%)	15 (38.5%)
Current employment status		
Working	18 (47.4%)	20 (51.3%)
Pensioned	1 (2.6%)	9 (23.1%)
Unemployed	11 (28.9%)	7 (17.9%)
House wife	3 (7.9%)	3 (7.7%)
Disabled	5 (13.2%)	
Last/current occupation		
Professional	6 (16.2%)	7 (18.9%)
Administrative	5 (13.5%)	6 (16.2%)
Clerical	10 (27.0%)	1 (2.7%)
Sales workers	2 (5.4%)	5 (13.5%)
Service workers	5 (13.5%)	7 (18.9%)
Production workers	4 (10.8%)	11 (29.7%)
No class	5 (13.5%)	

Table 2. Demographic characteristics (ITT safety)

	Milnacipran + Pindolol $n = 39$	Milnacipran + Placebo $n = 39$
Age (years)		
Mean (SD)	31.9 (8.1)	32.3 (10.0)
Min/max	18/51	18/51
Gender		
Male	17 (43.6%)	19 (48.7)
Female	22 (56.4%)	20 (51.3%)
Weight (kg)		
Mean (SD)	70.2 (12.9)	72.6 (12.8)
Min/max	47/98	51.7/107.9

Table 3. Baseline clinical characteristics

	Milnacipran + Pindolol $n = 39$	Milnacipran + Placebo $n = 39$
Melancholic	18	12
Severity moderate	18	17
Severity severe	21	22
Agitation	31	36
Retardation	6	2

Table 4. Past history of depressive disorder

	Milnacipran + Pindolol $n = 39$	Milnacipran + Placebo $n = 39$
Major depression before	16	17
Duration of the depressive disorder		
Mean SD (years)	3.1 (5.8)	5.4 (8.7)
Age at depressive disorder		
Mean (SD)	28.8 (7.6)	26.9 (9.2)
Suicide attempt	13	21 (χ test = p0.07)
Family history of depression	11	17

Table 5. MADRS mean scores (SD) (ITT, LOCF)

Visit number (Day)	Milnacipran + Pindolol $n = 39$	Milnacipran + Placebo $n = 39$
V2 (D0)	32.1 (6.2)	32.5 (6.4)
V3 (D4)	27.4 (8.6)	28.6 (6.8)
V4 (D7)	22.5 (10.0)	27.2 (8.2)
V5 (D10)	18.6 (10.1)	26.4 (9.0)
V6 (D14)	17.0 (9.3)	23.3 (9.9)
V7 (D21)	13.8 (8.1)	22.3 (10.7)
V8 (D28)	12.8 (8.7)	21.7 (11.5)
V9 (D42)	10.9 (6.3)	21.0 (11.5)

Table 6. HDRS, ITT

Visit number (Day)	Milnacipran + Pindolol $n = 39$	Milnacipran + Placebo $n = 39$
V2 (D0)	25.3 (6.9)	25.5 (7.1)
V3 (D4)	20.9 (7.8)	22.5 (8.3)
V4 (D7)	18.1 (8.5)	23.5 (7.6)
V5 (D10)	13.0 (8.4)	20.2 (7.9)
V6 (D14)	12.9 (7.6)	19.1 (8.5)
V7 (D21)	9.8 (5.6)	18.5 (8.6)
V8 (D28)	9.9 (6.8)	17.5 (8.3)
V9 (D42)	8.8 (5.6)	16.3 (9.5)

Table 7. CGI improvement, ITT AT DAY 42

	Milnacipran + Pindolol		Milnacipran + Placebo	
	n	%	*n*	%
Very much improved	27	75	8	24.2
Much improved	8	22.2	12	36.4
Minimally improved	1	2.8	5	15.2
No change			6	18.2
Minimally worse			1	3
Much worse			1	3
Very much + much improved	35	97.2	20	60.6

Table 2. Clinical baseline characteristics are shown in Table 3. There were no differences between groups. Table 4 shows the patients' past psychiatric history.

Tables 5 and 6 show MADRS and HDRS mean scores for both groups, respectively.

Improvement in MADRS total score was greater in the pindolol group than in the placebo group from day 7 (mean changes from baseline were −9.6 and −5.3, respectively, $p = 0.03$).

Table 7 shows CGI improvement by group. Responder rates in clinical global impression were 97.2% for the pindolol group and 60.6% for the placebo group.

Table 8 shows the most frequently observed adverse events. The distribution was similar, with no significant difference between the two treatment groups. Adverse events were mainly gastrointestinal disorders (nausea in 25 patients, vomiting in 12 patients).

Table 9 includes changes in blood pressure and heart rate for both groups. Vital signs were not modified during the study, and the evolution was not significantly different between the two treatment groups.

DISCUSSION

Milnacipran proved to be a well-tolerated and effective treatment of depression. However, the higher number of responders, together with an apparent

Table 8. Adverse events (ITT safety)

	Milnacipran + Pindolol $n = 39$	Milnacipran + Placebo $n = 39$
Nausea	11	14
Hot flushes	6	2
Sweating increased	5	5
Dizziness	3	2
Headache	3	4
Insomnia	3	1
Constipation		3
Vomiting	3	9
Influenza-like symptoms	3	4
Paraesthesia	2	1
Impotence	2	
Suicide attempt	2	4
Diarrhoea	2	4
Abdominal pain	2	

Table 9. Vital signs change mean (SD) (D42-baseline)

	Milnacipran + Pindolol $n = 39$	Milnacipran + Placebo $n = 39$
SBP (mmHg)	−3.3 (13.0)	−1.2 (12.7)
DBP (mmHg)	−2.3 (8.5)	1.6 (12.6)
HR (bpm)	−0.5 (11.5)	2.2 (12.0)

potentiation of antidepressant effect, in the pindolol combination group would seem to encourage further use of pindolol as an augmentation therapy in the treatment of depression. But in the milnacipran group there were more patients with previous suicide attempts and a family history of depression.

The study population displayed a higher level of gastrointestinal side effects (28% of those receiving milnacipran and pindolol; 36% of those receiving milnacipran alone) than normally associated with milnacipran (11%). Although this is a surprisingly high figure, it was not reflected in an increase in drop out from the study, partly because the effects were sufficiently mild and transient for the subject to tolerate them, and partly because the increased efficacy made the comparatively minor symptoms a price worth paying for significant clinical improvement.

Variability in response has been one of the enigmas of the pindolol randomized studies. Our group (Tome and Isaac, 1998) showed this effect when two populations with a different reduction in antidepressant latency was discerned.

Perez *et al.* (1997) showed a more rapid response to the combination of fluoxetine and pindolol in patients whose depression was not resistant to treatment. Other studies, however (e.g. Berman *et al.*, 1997; Moreno *et al.*, 1997; Perez *et al.*, 2001) did not demonstrate an accelerated antidepressant response with the combination of fluoxetine and pindolol.

Bordet *et al.* (1998) showed an acceleration of the response to the antidepressant effect with the use of paroxetine (20 mg per day) and pindolol (15 mg per day).

Explanations for these discrepant effects of pindolol have been based on differences in the demographic characteristics of the trial patients (Isaac and Tome, 1997); but this is clearly not the whole story.

An examination of the combination of fluoxetine and mianserin compared with fluoxetine and pindolol in treatment resistant major depression (Maes *et al.*, 1999) suggested that both pindolol and mianserin augmented the efficacy of fluoxetine but only the combination mianserin and fluoxetine resulted in a more rapid onset of antidepressant action.

This lends support to the notion that a combination of noradrenaline and serotonin system activation can reduce the latency of onset of action of antidepressants.

Moreover, imaging studies using PET technology have shown that occupancy in dorsal raphé nuclei (DRN) may correspond with pindolol plasma variability levels. Martinez *et al.* (2000), for example, suggested using a dose of 15 to 25 mg of pindolol per day in humans to achieve between 30% and 40% dorsal raphé nuclei 5HT1A receptor occupancy. This implies that the doses of pindolol used in previous randomized studies may have been too low to achieve adequate therapeutic activity in the brain; perhaps contributing to the observation that different responses are observed across (and even within) studies.

In addition, Rabiner *et al.* (2000), also using PET scanning, have suggested that the affinity of pindolol for the pre-synaptic 5HT1A *auto*receptor is higher than for the *post*synaptic 5HT1A receptor at a dose of 5 mg. This difference has been highlighted in PET scanning in the rat (Gunn *et al.*, 1998; Hirani *et al.*, 1999).

The issue of pindolol concentration was further explored in a double-blind randomized study of fluoxetine and pindolol (Perez *et al.*, 1999) in which plasma pindolol levels were measured. At a dose of pindolol 2.5 mg three times a day (in combination with fluoxetine 20 mg per day), the concentration of pindolol was maximal at 3 days and remained stable to day 42. The mean value was (6 to 7 ng/ml (24–28 nM).

It appeared that patients with high plasma levels of pindolol responded more slowly to treatment, perhaps because pindolol loses its partial 5HT1A agonist activity at high concentrations and acts more as a

beta-adrenergic blocker. Beta-blockers are well known to cause depressive effects so that, although pindolol has not been associated with depression, it is possible that too much beta-blockade may attenuate the effect of the antidepressant (Newman-Tancredi *et al.*, 1998; Rasanen *et al.*, 1999).

On the other hand, the increased response of almost 100% to the pindolol–milnacipran combination observed here may be explained by the pharmacology of milnacipran, as an inhibitor of both noradrenaline and serotonin reuptake. This has been suggested in animal studies (Briley and Montgomery, 1998), in which increases of up to 100% noradrenaline and serotonin firing have been observed when pindolol is added to milnacipran.

The clinical question of how long the combination of pindolol and antidepressant should be continued has been debated by Zanardi *et al.* (1997) in a 2, 4, 6 week study. Tome and Isaac (1998) followed up the patients for a year. The balance of the current evidence is that the combination must be used at least until a response to treatment has been achieved (commonly about 4 weeks).

We earlier suggested (Tome *et al.*, 1997a) that personality variables along the lines of Cloninger's (1987) typology may be important predictors of treatment response. In that previous study we indicated those patients with novelty seeking characteristics were more likely to show an accelerated response to pindolol augmentation. A comparable analysis of personality variables in the present study is underway.

In conclusion, pindolol appears to be effective in reducing the onset of action of the antidepressant, as well as potentiating its effect in some circumstances. There is no evidence that pindolol at 7.5 mg per day has any effect on the cardiovascular system of our patients as judged by the vital signs. Pindolol overdose is potentially hazardous, but one of our patients took up to 70 mg of pindolol and 400 mg of milnacipran and showed no clinically significant changes in ECG and did not require medical intervention.

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