

# Milnacipran, a Well-Tolerated Specific Serotonin and Norepinephrine Reuptake Inhibiting Antidepressant

M. Briley

*Institut de Recherche Pierre Fabre, Parc Industriel de la Chartreuse,  
81100 Castres, France*

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## INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) were developed with the idea of removing from the pharmacological profile of tricyclic antidepressants (TCA) all of the activities which were thought to be responsible for their adverse effects. Thus interactions with the muscarinic cholinergic receptor, the histamine receptor, and the  $\alpha_1$  adrenoceptor were avoided. In addition, the ability to inhibit the reuptake of norepinephrine was also excluded from the mechanism of this new class of antidepressants, probably to eliminate potential cardiovascular effects. This strategy of selectivity has clearly been beneficial in terms of adverse effect rates, which are lower for SSRIs than for TCAs. In retrospect, however, the selectivity for a single monoamine was not the best strategy and tends to result in a lesser efficacy than that of TCAs, especially in severe or endogenous depression. This is suggested, for example, by the demonstration, in controlled studies that the TCA clomipramine is significantly superior to citalopram (10) or paroxetine (11) in endogenously depressed patients. General clinical opinion appears to confirm the findings of these trials. A recent survey of Swedish psychiatrists, for example, showed that 80% of those questioned considered that SSRIs were not equivalent to TCAs in severe depression (25).

Milnacipran<sup>1</sup> was thus developed as a new specific serotonin and norepinephrine reuptake inhibitor (SNRI) with the intention of providing greater antidepressant efficacy than the SSRIs without the side effects of the TCA (7). This article reviews the preclinical properties, pharmacokinetics, and principal clinical and safety data of milnacipran.

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<sup>1</sup>Milnacipran (Ixel®) has recently been launched in France and is currently being registered throughout Europe.

Address correspondence and reprint requests to Dr. M. Briley, Institut de Recherche Pierre Fabre, Parc Industriel de la Chartreuse, 81100 Castres, France. Fax: +33 (563) 72 50 66.

## MECHANISM OF ACTION

### Neurochemistry

Milnacipran (30,6) inhibits the reuptake of both serotonin and norepinephrine with approximately equal potency ( $IC_{50}$  values of 203 and 100 nM for the inhibition of serotonin and norepinephrine uptake, respectively, in rat hypothalamic slices) (27) with no effect on the reuptake of dopamine.

The extracellular levels of both serotonin and norepinephrine, measured by microdialysis in the hypothalamus of freely moving guinea pigs, were increased several-fold by milnacipran 10 mg/kg i.p. (29), whereas the monoamine metabolites 5-hydroxyindoleacetic acid (5-HIAA) and 4-hydroxy-3-methoxyphenyl-glycol (MHPG) (produced by the intracellular action of monoamine oxidase) were decreased by about 50%. These results demonstrate that milnacipran inhibits the uptake of the two monoamines with similar potency *in vivo* as *in vitro* (27).

The rate-limiting enzymes for the synthesis of serotonin and norepinephrine, tryptophan and tyrosine hydroxylase, respectively, are highly sensitive to feedback control by increased extracellular concentrations of their monoamine products. They are thus sensitive *in vivo* markers of increased monoaminergic activity. In the frontoparietal cortex of the rat, milnacipran induced a decrease in the synthesis of both monoamines (28), consistent with an increase in both serotonergic and noradrenergic activity. Chronic administration of milnacipran led to a significant increase in the basal synthesis of both serotonin and norepinephrine (28).

Milnacipran does not bind to any neurotransmitter receptor tested. Binding affinities, expressed as  $IC_{50}$  values, were greater than  $10^{-5}$  M for the 40 receptors studied (27 and unpublished data). In particular, and in contrast to the TCAs, there was no affinity for  $\alpha_1$  adrenoceptors, muscarinic cholinergic or  $H_1$  histamine receptors which are thought to be responsible for the orthostatic hypotension, anticholinergic effects (dry mouth, constipation, blurred vision), and sedation seen with TCAs.

A number of studies from various laboratories (31) have confirmed the original observations (5,27) that, unlike many antidepressant drugs, repeated administration of milnacipran does not result in downregulation of  $\beta$  adrenoceptors. There is also no effect on the  $\beta$  adrenoceptor-linked adenylate cyclase or on  $\beta$  adrenoceptor-mediated behavior such as salbutamol-induced hypoactivity in mice (4). Since milnacipran inhibits the reuptake of norepinephrine and increases the extracellular levels of norepinephrine *in vivo* as measured by microdialysis, it is rather surprising that there is no influence on  $\beta$  adrenoceptor sensitivity. For the moment, there is no clear explanation. This phenomenon does, however, reinforce the idea that  $\beta$  adrenoceptor downregulation, produced by many antidepressants, is unrelated to the therapeutic potential of these compounds. In addition, when administered repeatedly, milnacipran produced no alterations of  $\alpha_1$  or  $\alpha_2$  adrenoceptors, 5-HT<sub>1</sub> or 5-HT<sub>2</sub> receptors, or benzodiazepine binding sites which are modified by certain antidepressants. Moreover, uptake and accumulation of serotonin and norepinephrine were unmodified and the potency for milnacipran to inhibit monoamine uptake *in vitro* in the cortex remained unaltered (5).

## Psychopharmacology

Milnacipran was active in behavioral tests involving the noradrenergic system, such as antagonism of tetrabenazine-induced hypothermia and inhibition of yohimbine-induced mortality, as well as in tests involving the serotonergic system, such as potentiation of 1-tryptophane-induced behavior (40). Milnacipran is neither stimulant nor sedative in classical tests, and has no anticholinergic effects. The slight mydriasis produced by milnacipran was completely antagonized by the  $\alpha_1$  adrenoceptor antagonist prazosin. This shows the effect to be the result of a sympathetic noradrenergic stimulation and not a parasympathetic cholinergic inhibition.

Milnacipran is active in three widely used models of depression, the behavioral despair (Porsolt) test (unpublished), the learned helplessness test (19), and the bulbectomized rat model (37).

## HUMAN PHARMACOKINETICS

The pharmacokinetics and metabolism of milnacipran have been the subject of a recent review (34). The use of [ $^{14}\text{C}$ ]milnacipran has shown that more than 90% of the dose is recovered in urine over 96 h, while the fecal elimination represents less than 5% of total elimination. The elimination is rapid, with approximately 85% of the initial dose being recovered within the first 24 h. The absolute oral bioavailability, assessed in a cross-over design with intravenous infusion, shows that the plasma profiles of milnacipran 50 mg given either i.v. or p.o. are similar, and are indistinguishable 2 h after administration (35).

Milnacipran is absorbed rapidly, with peak plasma concentrations between 0.5 to 4 h after oral administration. The mean maximum concentration after the administration of 50 mg is approximately 120 ng/ml, with an inter-individual variations of less than 3-fold. The pharmacokinetics of orally administered milnacipran best fit a two-compartment model with the terminal phase lasting more than 36 h after drug intake (35). Following twice daily administration, the steady-state plasma concentration is reached within 2 to 3 d, with peak levels 70 to 100% greater than after an acute dose. Plasma concentrations are linearly proportional with dose over the range of single acute doses of 25 to 200 mg. Plasma protein binding of milnacipran, evaluated over a concentration range up to 10 times therapeutic blood levels, was low (13%) and non-saturable. The volume of distribution for milnacipran is  $5.3 \pm 0.4$  l/kg, which is in the same range of magnitude of many SSRIs (e.g., fluvoxamine, paroxetine) and venlafaxine. In general, larger volumes of distribution are associated with TCAs (10 to 30 l/kg) (22).

Milnacipran and its glucuronide conjugate are the principle components circulating in plasma, while N-dealkylated milnacipran is present only in very low concentrations. In urine, the main route of elimination, 50 to 60% of the dose is recovered as parent drug and approximately 20% as the glucuronide conjugate of milnacipran. The remainder is essentially N-dealkylated milnacipran and its glucuronide conjugate. Only an insignificant proportion of the dose is excreted as other metabolites. None of the metabolites of milnacipran has any pharmacological active at the levels found clinically.

The metabolism of milnacipran is qualitatively unchanged at doses up to 4 times the therapeutic dose (36) suggesting that the metabolic capacity of the liver is unlikely to be exceeded in the case of (at least moderate) accidental or intentional overdose (see section on tolerance).

Cytochrome P450 2D6 is involved in the metabolism of many psychotropic drugs (18,32) and its inhibition is frequently a cause of drug-drug interactions. This enzyme is not, however, implicated in the metabolism of milnacipran and no oxidative metabolites of milnacipran have been detected in humans.

The elimination half-life of milnacipran is approximately 8 h (35). The liver and kidneys are both involved in the elimination of milnacipran as illustrated by renal and non-renal clearances with values of  $23.8 \pm 7.3$  and  $16.4 \pm 3.1$  l/h, respectively (35). This balance between renal and non-renal clearances may be an advantage in patients presenting with moderate renal insufficiency.

The pharmacokinetics of milnacipran has been studied in chronically renally impaired patients (34) characterized by creatinine clearance values which ranged from 10 to 85 ml/min. A 2- to 4-fold increase in parent drug, as well as in the glucuronide conjugate, was observed in plasma in this group. This increase was proportional to the degree of renal impairment. The terminal half-lives ranged from 9 to 25 h, compared with  $8.3 \pm 0.9$  h for the control group. As the apparent volume of distribution was not altered, the increase in half-life resulted from a decrease in apparent total clearance. The quantity of drug recovered in urine over a fixed time period was reduced proportionally to the degree of renal impairment. A highly significant correlation was demonstrated between apparent total clearance or renal clearance of milnacipran and creatinine clearance. It is thus straightforward to determine the appropriate dose reduction in renally impaired patients. A 25-mg capsule is available to allow dose adjustment in such patients.

Glucuronide conjugation is not appreciably affected by decreased liver function and there was no change in the pharmacokinetic profile of milnacipran in patients with alcoholic cirrhosis. Decreased liver and kidney functions and changes in the fat/muscle ratio often modify the pharmacokinetics of drugs in the elderly. Milnacipran administered to elderly patients aged 68 to 91 years gave time to peak plasma concentrations similar to those observed in younger healthy volunteers. The maximum concentration and area under the curve (AUC) of milnacipran were, however, slightly increased (+20%) in the elderly. The elimination rate was decreased by 10%, but the amount of drug excreted in urine was similar to that found in healthy volunteers. These differences in pharmacokinetic parameters were minor, however, so that no dose adjustment is recommended in the elderly, except in those with moderate to severe renal impairment (see above).

Since milnacipran possesses low and non-saturable plasma protein binding activity and is not metabolized via the liver cytochrome P450 system, few drug-drug interactions are expected. Indeed, no significant interactions (< 20% modification of plasma levels) have been observed with lithium, lorazepam, levomepromazine, or carbamazepine.

## CLINICAL STUDIES

### Efficacy

The efficacy of milnacipran has been demonstrated in three placebo-controlled studies (Table 1). All three studies, as well as subsequent comparator trials, involved patients meeting criteria for major depression according to DSM-III or DSM-III-R. Efficacy was assessed using the 17-item Hamilton Depression Rating Scale (HDRS) (16) and/or the Montgomery Asberg Depression Rating Scale (MADRS) (26) as well as the Clinical Global Impression (CGI). In the first study (24), milnacipran 50 mg b.i.d. was more effective than placebo in 58 patients who were hospitalized for severe depression (MADRS > 25). A significant difference was observed on the MADRS at 2 w ( $p < 0.05$ ) and at 4 w ( $p < 0.01$ ). Similar results were observed on the HDRS and on the secondary efficacy measures.

The second study (20) was carried out in hospitalized endogenously depressed patients and compared 41 patients in the placebo group with 60 receiving milnacipran 50 mg b.i.d. (per protocol population). A significant difference between milnacipran and placebo ( $p < 0.05$ ) was observed on the HDRS at endpoint. The difference on the MADRS was also in favor of milnacipran but it did not reach statistical significance.

In the third study (20), carried out in the U. S. in ambulatory patients, three fixed doses of milnacipran (25, 50, and 100 mg b.i.d.) were compared with placebo. The lowest dose, 25 mg b.i.d., was not significantly different from placebo, 50 mg b.i.d. and 100 mg b.i.d. were both effective. The patients in the group receiving 50 mg b.i.d. were significantly more improved than those on placebo, as judged by the change from baseline on the MADRS ( $p < 0.01$ ) and the HDRS ( $p < 0.05$ ), whereas the patients receiving 100 mg b.i.d. were significantly better only on the MADRS. This study helped establish 50 mg b.i.d. as the minimum effective dose of milnacipran. No

TABLE 1. Double-blind trials comparing milnacipran (mln) 50 mg b.i.d. with placebo and reference antidepressants

Comparator	Duration	Number of patients mln 50/comparator	Type of patients
Placebo	4 weeks	29/29	hospitalized
Placebo	6 weeks	68/49	endogenous; hospitalized
Placebo	8 weeks	130/133	out-patients
Imipramine (75 mg b.i.d.)	6 weeks	50/50	hospitalized
Imipramine (50 mg b.i.d.)	8 weeks	112/109	elderly hospitalized and out-patients
Imipramine (75 mg b.i.d.)	6 weeks	54/59	hospitalized
Imipramine (75 mg b.i.d.)	6 weeks	55/64	endogenous; hospitalized
Imipramine (75 mg b.i.d.)	6 weeks	53/56	hospitalized
Imipramine (75 mg b.i.d.)	6 weeks	30/34	hospitalized
Fluoxetine (20 mg o. d.)	12 weeks	93/100	endogenous; hospitalized
Fluvoxamine (100 mg b.i.d.)	6 weeks	57/56	hospitalized and out-patients

clear extra improvement was seen between the 50 mg and 100 mg b.i.d. groups, both of which were significantly more effective than 25 mg b.i.d.

Placebo-controlled studies thus suggest that milnacipran 50 mg b.i.d. is efficacious in treating depression in ambulatory or hospitalized patients with moderate to severe depression, with or without endogenous features. Examination of the qualitative nature of the response to milnacipran showed that it acts consistently on all core symptoms of depression (anxiety, memory, sleep disorders, and retardation) without producing either sedation or the emergence of suicidal thoughts (33).

Two trials have compared milnacipran to amitriptyline. In a 4-week study, milnacipran 25 and 50 mg b.i.d. were compared with amitriptyline 75 mg b.i.d. (1). Milnacipran, 25 mg b.i.d., was less effective, while 50 mg b.i.d. had efficacy similar to that of amitriptyline. Another study by the same group (2) showed no significant difference in the outcome of patients treated with milnacipran 100 mg b.i.d. or amitriptyline 75 mg b.i.d. The results of these trials are consistent with the dose-dependency demonstrated in the placebo-controlled trials.

Milnacipran has been compared to clomipramine in three studies, although only one study used the optimal dose (50 mg b.i.d.) of milnacipran. This 3-month study (8), which compared milnacipran 50 mg b.i.d. with clomipramine 75 mg b.i.d. in a group of endogenously depressed hospitalized patients, showed no significant difference in the improvement in any of the outcome criteria produced by either milnacipran or clomipramine. Milnacipran was, however, better tolerated than clomipramine. A small 6-month trial (21) comparing milnacipran 100 mg b.i.d. with clomipramine 75 mg b.i.d. showed no significant difference at endpoint in the treatment effects of the two antidepressants on the MADRS or the CGI scales; the HDRS showed a small but significant difference in favor of clomipramine. Milnacipran was again better tolerated than clomipramine. The third trial compared milnacipran with clomipramine over 6 months in a group of treatment-resistant patients (39). Milnacipran and clomipramine were titrated to 100 mg b.i.d. and 75 b.i.d., respectively, during the first week and then kept constant for the next 9 weeks. After this time, dose adjustment was allowed for both drugs. There was no significant difference in any of the outcome criteria between the two antidepressants, although no more than a third of the patients responded (50% decrease in the HDRS) in either group.

Milnacipran has been compared to imipramine in an 8-week study in elderly patients (41). Doses were increased progressively to 50 mg b.i.d. of milnacipran or imipramine in 219 patients aged 65 to 93 years. At the end of the treatment (8 weeks) there was no difference in the antidepressant effect in the two groups. A significantly greater number of adverse effects were seen, however, in the imipramine group. The authors concluded that milnacipran may be preferable to imipramine in elderly depressed patients as it provides the same antidepressant activity as imipramine with a lower incidence of side effects and does not impair cognitive ability (41).

A number of other studies comparing milnacipran with imipramine have not yet been published in detail (see 17 for review), but have been analyzed together as a meta-analysis (see below).

An early study (3) found milnacipran 100 mg given as a single daily dose to be significantly less efficacious than fluoxetine 20 mg. This result has been attributed (23), however, to the inappropriate dose regime of once-daily administration of milnacipran; the half-life of this drug is ~8 h, and once-daily administration is unlikely to

maintain adequate levels of the compound. A more appropriately designed study (15) compared milnacipran 50 mg b.i.d. and 100 mg b.i.d. to fluoxetine 20 mg once daily over 12 w in a total of 289 hospitalized patients with endogenous depression. Both the HDRS and the MADRS showed the order of antidepressant efficacy to be milnacipran 50 mg b.i.d. > milnacipran 100 mg b.i.d. > fluoxetine 20 mg, although there was no overall statistically significant effect. Time by time analysis, however, showed a consistent trend for milnacipran 50 mg b.i.d. to be superior to fluoxetine 20 mg, a difference which was statistically significant at day 28 on several converging parameters. The side effect profiles of milnacipran and fluoxetine were essentially similar.

A 6-week study has compared milnacipran 50 mg b.i.d. with fluvoxamine 100 mg b.i.d. in a population of 113 hospitalized and ambulatory depressed patients. This study, which has yet to be published in detail (see 23 for review), showed that, at endpoint, milnacipran produced a significantly greater decrease in the MADRS score than fluvoxamine. The effect of the HDRS showed a trend in favor of milnacipran which did not reach the level of significance.

Double-blind, randomized, controlled studies comparing an antidepressant with placebo or comparator medication often have insufficient statistical power to fully test for efficacy. This problem can be addressed by pooling comparable studies into large meta-analyses which provide sufficient patient numbers to avoid type II errors. A limitation of meta-analyses is, however, that patient populations may not be identical. The results should thus be taken as indicative rather than fully demonstrative.

A meta-analysis has been performed on the original data of the three principal placebo-controlled studies of milnacipran 50 mg b.i.d. (33) (Table 1) using an intent-to-treat analysis of all randomized patients based on the last observation carried forward for patients not completing the trial. This analysis shows milnacipran to be significantly superior to placebo on the principal efficacy criteria (Table 2). At endpoint the global treatment effects (calculated from the adjusted means) were 3.7 points greater on the MADRS with milnacipran than with placebo and 2.3 points greater on the HDRS (33). Based on the criteria of the European consensus group, (14) these differences are considered to be clinically as well as statistically significant.

The largest homogeneous group of comparator studies is represented by six studies comparing milnacipran 50 mg b.i.d. with imipramine (17) (Table 1), involving 726 patients, most of whom were hospitalized at the beginning of the studies. In five trials, imipramine was used at the recommended dose of 150 mg/d (75 mg b.i.d.). In the remaining study in elderly patients (41), 100 mg/d (50 mg b.i.d.) was used. A meta-analysis of the original data of these studies (Table 2) shows that milnacipran and imipramine have comparable efficacy measured on the HDRS, with a mean response rate of 63.9% for milnacipran and 66.0% rate for imipramine. Results with the MADRS were similar. As expected, milnacipran was significantly better tolerated, with 7.6% withdrawal due to side effects for milnacipran and 14.8% for the TCA.

Lopez-Ibor et al. (23) have reviewed the two major studies that have compared milnacipran 50 mg b.i.d. with the SSRIs fluoxetine (20 mg/d) (15) and fluvoxamine (100 mg b.i.d.). A meta-analysis of the original data of these studies, again using weighted means of the observed values from an intention-to-treat analysis of all randomized patients (Table 2) shows milnacipran to be significantly more effective than the SSRI on the main efficacy criteria on both the MADRS and HDRS. The weighted means showed a difference in favor of milnacipran of 2.6 and 4.2 points on the HDRS

TABLE 2. Summary of meta-analyses of double blind trials comparing milnacipran 50 mg b.i.d. with placebo and comparator antidepressants

	HDRS								MADRS					
	N	baseline	endpoint	p	Responders		Remission		N	baseline	endpoint	p	Responders	
					%	p	%	p					%	p
Placebo	211	25.7 ± 0.2	16.1 ± 0.6		40.3		20.4			31.4 ± 0.4	20.0 ± 0.9		39.8	
Milnacipran	227	26.2 ± 0.0	13.7 ± 0.6	0.01	54.6	< 0.01	26.4	ns		31.7 ± 0.4	16.2 ± 0.8	< 0.01	52.4	< 0.01
Imipramine	338	25.5 ± 0.3	11.1 ± 0.5		66.0		41.1		313	33.8 ± 0.3	14.1 ± 0.7		65.2	
Milnacipran	324	25.9 ± 0.3	12.0 ± 0.5	ns	63.9	ns	37.7	ns	300	34.5 ± 0.3	15.8 ± 0.7	ns	62.7	ns
SSRI	156	26.5 ± 0.4	14.3 ± 0.8		50.0		27.6			32.8 ± 0.5	17.9 ± 1.1		51.3	
Milnacipran	150	27.0 ± 0.4	11.9 ± 0.8	0.02	64.0	0.01	38.7	0.04		33.5 ± 0.5	14.2 ± 1.0	< 0.01	67.3	< 0.01

The values given are the weighted means of the observed values determined by an intention-to-treat analysis of all randomized patients. The statistical

and MADRS, respectively. These differences are not only statistically significant but are also clinically very significant (14). Interestingly, venlafaxine, another SNRI, has also shown significant superiority over the SSRI fluoxetine (9, 12).

### Tolerance Profile

An analysis of the complete clinical database of milnacipran (> 4000 patients with 434 patients aged over 65 years) shows that milnacipran 50 mg b.i.d. is better tolerated than milnacipran 100 mg b.i.d. (33), confirming that 50 mg b.i.d. is the preferred dose for most patients when both efficacy and tolerability are considered.

Considering only the patients involved in studies using 50 mg b.i.d. milnacipran, 1871 patients have been treated with milnacipran, 940 with a TCA, 344 with an SSRI, and 394 with placebo. Drop-outs for adverse effects were 7.6% with milnacipran, 14.8% with a TCA, 7.8% with an SSRI, and 6.1% for placebo.

Patients receiving milnacipran reported five adverse effects significantly more frequently than patients on placebo (vertigo 5.0%, increased sweating 4.3%, anxiety 4.1%, hot flushes 3.0%, and dysuria 2.1%). Patients receiving TCAs reported seven adverse effects significantly more frequently than placebo (dry mouth 37.3%, constipation 14.9%, tremor 12.8%, sweating 12.2%, somnolence 10.5%, tiredness 8.9%, vertigo 8.7%). All of these adverse effects were significantly more frequent than with milnacipran. Patients receiving SSRIs had significantly more nausea (20.1%) than those receiving milnacipran, TCA, or placebo. Only dysuria (2.1%) was seen more frequently with milnacipran than with the TCAs or SSRIs (33). Adverse events appearing with placebo, milnacipran, TCAs, and SSRIs are shown in [Table 3](#).

Milnacipran is thus clearly better tolerated than TCAs and similarly to SSRIs. The reduced incidence of adverse effects with milnacipran is probably a result of its pharmacological selectivity and, in particular, its lack of interaction at postsynaptic receptors (27). The absence of any antagonism of the  $\alpha_1$  adrenoceptors by milnacipran is reflected in decreased frequency of tiredness as compared with TCAs. However, the absence of  $\alpha_1$  adrenoceptor antagonism allows an increase in noradrenergic tone, which is probably responsible for the dysuria that is more common with milnacipran than with the TCAs. This adverse effect needs to be monitored carefully in male patients with prostatic adenoma and justifies contraindication in patients where symptoms of dysuria are already present.

The hemodynamic effects of milnacipran are similar to those of TCAs, with a mild increase in heart rate (3 to 4 bpm) with both compounds and a negligible effect (< 1 mm Hg) on blood pressure. In contrast, the incidence of orthostatic hypotension (a decrease of > 20 mm Hg) was higher with TCAs (34%) than with milnacipran (21%). TCAs and milnacipran also differ in their electrophysiological effects with the PR interval, the QRS duration, and the corrected QT space being significantly increased with TCAs but unchanged with milnacipran.

Analysis of long-term safety (715 patients on milnacipran for more than 6 months, 189 for more than a year) has shown that most adverse events appear within the first 3 months of treatment and the incidence decreases regularly thereafter. Importantly, no new emergent adverse events developed with long-term treatment (33).

Fifteen cases of intentional overdose of milnacipran were reported during clinical trials, with ingested quantities of up to 2800 mg taken either alone or in association

with other therapeutic agents. There have been no deaths and the outcome of these incidences has been favorable in all cases. Since its commercialization in France, quantities of up to 5600 mg of milnacipran (two month's supply) has been taken in intentional or accidental overdose with no serious consequences.

## CONCLUSIONS

Milnacipran is a selective serotonin and norepinephrine reuptake inhibitor with no action at any pre- or postsynaptic receptors. It is rapidly and extensively absorbed when taken orally. It has an intermediate half-life of about 8 h and no active metabolites. Unlike many antidepressants it does not modify, and is not affected by, the cytochrome P450 system.

The antidepressant efficacy of milnacipran has been demonstrated in three placebo-controlled studies. Its efficacy in severely ill, hospitalized patients is comparable to that seen with TCAs such as imipramine. A meta-analysis of studies comparing milnacipran with the SSRIs fluoxetine and fluvoxamine has shown milnacipran to be significantly more effective with an effect size that is clinically meaningful. The superior efficacy of milnacipran compared with the SSRIs is similar to that reported for other antidepressants inhibiting the reuptake of both serotonin and norepinephrine, such as the TCA clomipramine (10,11) and another SNRI venlafaxine (12). There is accumulating evidence that SNRI (7) and other double-action antidepressants (38), which act to increase both noradrenergic and serotonergic neurotransmission, show superior efficacy over the SSRIs. This suggests that a simultaneous double action on serotonin and norepinephrine neurotransmission may be associated with superior efficacy compared with the more selective action on serotonin alone (7).

TABLE 3. Incidence (%) of spontaneously reported adverse effects in patients with major depression receiving placebo, milnacipran, SSRI, or TCA

	Placebo (n = 395)	Milnacipran (n = 1871)	SSRI (n = 344)	TCA (n = 940)
Nausea	10.9	11.2	20.1	8.4
Headache	17.0	8.4	4.1	9.7
Dry mouth	5.6	7.9	3.8	37.3
Abdominal pain	5.1	6.5	8.7	5.5
Constipation	4.3	6.5	5.2	14.9
Insomnia	10.7	6.1	4.7	6.9
Vertigo	1.8	5.0	3.5	8.7
Increased sweating	1.3	4.3	2.6	12.2
Anxiety	1.3	4.1	5.8	3.9
Tremor	1.5	2.5	3.5	12.8
Tiredness	3.0	2.5	2.9	8.9
Somnolence	3.8	2.3	2.9	10.5

All adverse events reported by more than 5% of the patients in any treatment group are included.

The efficacy of milnacipran is similar to that of the TCA imipramine (Table 2), and milnacipran also has good general and cardiovascular tolerance and safety even when overdosed; this drug represents, therefore, a useful alternative to TCAs. Milnacipran and SSRIs have comparable safety and tolerance, but the superior efficacy of milnacipran (Table 2) gives the SNRI a more favorable benefit/risk ratio.

In addition, milnacipran is clearly effective across the full spectrum of major depression regardless of type, severity, or hospitalization. This makes milnacipran particularly interesting as a first-line treatment where its extra efficacy and low side effect profile make it a drug of choice in most situations.

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