Japanese experience with milnacipran, the first serotonin and norepinephrine reuptake inhibitor in Japan

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Abstract: Milnacipran is a serotonin and norepinephrine reuptake inhibitor (SNRI), with a balanced potency for the inhibition of the reuptake of the two monoamines. In this, it contrasts with venlafaxine and duloxetine which, while possessing a dual action, have a selectivity of the order of 30-fold and 10-fold respectively for the reuptake of serotonin. Milnacipran has mainly been launched in countries where the selective serotonin reuptake inhibitors (SSRIs) and venlafaxine had been established for several years. As such it has attracted relative little interest from clinician investigators as a research tool. Japan, however, represents a unique situation because in 1999 milnacipran was launched within months of the first SSRI and is still the only SNRI in Japan together with only two SSRIs (a third has just been introduced). This has led to a large number of investigative clinical studies, many of which give interesting insights into the potential of milnacipran in the treatment of depression and of other disorders. This article reviews these Japanese studies with milnacipran.

Keywords: depression, antidepressants, SNRI, pain

Introduction

The treatment of depression in Japan

"Life means suffering" is the first of the four noble truths of Buddhism and for over 15 centuries this religion/philosophy has encouraged the acceptance of suffering and sadness and discouraged the pursuit of happiness. In Japanese mythology stories rarely have "a happy ending" while sadness and suffering are both noble and omnipresent. This may go some way to explaining why mental illness has never been adequately addressed in Japan.

The Japanese word for depression, "utsubyo," traditionally refers only to severe or bipolar depression. In fact, until recently, depression was considered in the same way as schizophrenia, and treated only in specialized institutions.

Although there are no nationwide epidemiological data for depression in Japan, a small-scale survey found that, based on the Center for Epidemiological Studies Depression (CES-D) criteria, 13% of men and 16% of women had depressive symptomatology with 4.5% and 9.4%, respectively, having moderate or severe depressive symptoms (Miyaji et al 1994). Another small survey (Kawakami et al 1996), using the DSMIII-R (Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised) criteria in a cohort of 140 Japanese workers found 6-month and lifetime prevalence rates of major depressive episodes to be 4% and 14%, respectively. More recently the World Mental Health Japan Survey made a 12-month survey (2002–2003) of 1663 persons from four areas (two urban and two rural) of Japan (Kawakami et al 2005). Using the World Health Organization Composite International Diagnostic Interview (WMH-CIDI) the survey found a 12-month prevalence of major depression of only 2.9%. Both of these studies suggest

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a prevalence considerably lower than in Western countries where the Depression Research in European Society study (DEPRES) found a 6-month prevalence of 17% (Lepine et al 1997). Another survey in Japan (Kawakami et al 2004), which also found a relatively low incidence of depression in a sample of 1029 urban Japanese, observed a greater risk of mood, anxiety, and alcohol use disorders among a recent birth cohort. Whether this reflects a change in prevalence of depression in the younger generation in Japan remains to be seen. A sign that the traditional view of depression as being rare in Japan may not be the whole story is the fact that Japan's suicide rate is one of the highest in the world, more than three times that of the UK, for example, and continues to increase each year (World Health Organization data).

In view of the traditional Japanese attitude to depression, it is not surprising that until recently, sales of antidepressants in Japan were minimal. Total annual sales of all antidepressants in Japan (population 125 million) in 1995 were just over US$150 million compared with more than US$2 billion in sales of fluoxetine alone in the USA (population 300 million) the same year. At that time only tricyclic antidepressants (TCAs) and a few "atypical" antidepressants such as mianserin were available in Japan.

In 1999 fluvoxamine was introduced into Japan as the first "modern" antidepressant. This selective serotonin reuptake inhibitor (SSRI) was rapidly followed by the serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI) milnacipran, and a second SSRI, paroxetine. These three remained the only "modern" antidepressants until July 2006 when sertraline was launched, ironically on the same day that it became generic in the USA. Escitalopram/citalopram, fluoxetine, venlafaxine, mirtazapine, and duloxetine are either still under development in Japan or have been "abandoned" for the Japanese market.

The introduction of the three "modern" antidepressants was accompanied by considerable effort to increase medical and public awareness of depression with a three-point message:

1. Depression is a disease from which anyone can suffer.
2. It can be successfully treated with drugs.
3. Early detection and the treatment of "mild" depressive symptoms improve prognosis.

Since the introduction of the three "modern" antidepressants in 1999/2000 the antidepressant market has expanded more than four-fold to US$650 million in 2005. Paroxetine is the clear market leader with approximately 50% of the market. The SNRI milnacipran comes second with 12.5% of the market, followed by fluvoxamine. Almost all of the increase in the antidepressant market is represented by sales of these three drugs.

Milnacipran in Japan—a unique situation

In Europe and elsewhere milnacipran has been systematically launched on a market where the SSRIs have been established for a number of years and where venlafaxine is usually the "reference SNRI." In Japan, however, milnacipran was launched within months of the first SSRI and is the only SNRI present on the Japanese market. In addition to the obvious commercial advantage of this situation, Japanese clinicians, who had been deprived of modern antidepressants for many years, finally had both SSRI and SNRI drugs to use and to investigate clinically. This has led to a large number of studies, most of them preliminary, many of which give interesting insights on the potential of milnacipran in the treatment of depression and of other disorders. This article will review these Japanese studies with milnacipran.

An extensive Medline search was carried out using "milnacipran" as a keyword and all publications by Japanese authors (based on the address given in the publications) were retained. Following our request, Pierre Fabre Médicament, manufacturers of milnacipran, and Asahi-Kasei, who sell milnacipran in Japan, supplied additional references. All original publications were retained for inclusion in this review. Articles in Japanese were only included where a substantial English language summary was available. No "qualitative" assessment of the publications was made.

Basic studies

Although a lot of basic studies had already been carried out before milnacipran was introduced onto the Japanese market (for review see Briley et al 1996), the subsequent enthusiasm of Japanese researchers has led to a number of significant pre-clinical contributions to our understanding of milnacipran.

Effects on monoamines and monoamine reuptake

The key characteristic of milnacipran, namely its equipotency for the inhibition of 5-HT and NE reuptake (Moret et al 1986), was confirmed in Japanese preclinical studies (Mochizuki et al 2002a) which showed that milnacipran selectively inhibited sodium-dependent 5-HT and NE uptake into the rat cerebral cortex synaptosomes with similar potencies and no effect on any neurotransmitter receptor.

Microdialysis studies in the medial prefrontal cortex showed that milnacipran caused a dose-related increase in the extracellular levels of 5-HT and NE with similar potency (Mochizuki et al 2002a). These results were similar to those obtained previously in guinea pig hypothalamus (Moret and Briley 1997). Another microdialysis study in the cell body regions (Bandoh et al 2004) showed that a single administration of milnacipran decreased the levels of NE and its metabolite, 4-hydroxy-3-methoxymandelic acid, in the locus coeruleus, and the levels of 5-HT and its metabolite, 5-hydroxyindole-3-acetic acid, in the dorsal raphe nucleus. Combined administration of milnacipran with either the α_2-adrenoceptor antagonist, yohimbine, or the 5-HT_{1A} receptor antagonist, WAY100635, reversed the milnacipran-induced decreases of NE and 5-HT, respectively, indicating that treatment with milnacipran causes negative feedback through stimulation of α_2-adrenoceptors and 5-HT_{1A} autoreceptors in the cell-body regions.

Treatment with milnacipran for 7 days results in a significant increase in the basal levels of extracellular NE in the medial prefrontal cortex in rats (Kitaichi et al 2005a). In addition acute administration of milnacipran following a 7-day treatment of milnacipran results in a greater increase in extracellular NE than a single acute administration of milnacipran alone. These results suggest that repeated milnacipran treatment enhances noradrenergic neuronal transmission beyond that achieved with acute administration alone. Interestingly, repeated administration of milnacipran had no effect on serotonergic or dopaminergic neurotransmission.

Cultured adrenal medullary cells have been used as an in vitro model for studying NE transporter function. In this model, prolonged exposure to milnacipran appears to increase NE transporter function (Shinkai et al 2005). As expected, an acute exposure with milnacipran resulted in a competitive inhibition of the NE transporter. Prolonged exposure with milnacipran, however, caused time- and concentration-dependent increases in NE uptake and NE transporter density with no increase in NE transporter mRNA. The addition of the ribosomal protein synthesis inhibitor, cycloheximide, abolished these effects (Shinkai et al 2005) suggesting that up-regulation of NE transporter function following prolonged exposure to milnacipran, probably results from post-transcriptional modifications.

In addition to neurons, glial cells have also been shown to express functional NE transporter sites and may exert significant control of noradrenergic activity by inactivating NE that escapes neuronal re-uptake at sites distant from terminals (Henn and Hamburger 1971). Milnacipran has been shown to inhibit the reuptake of NE by cultured rat cortical astrocytes, an experimental model of glial cells (Inazu et al 2003) with characteristics similar to those of neuronal reuptake.

Electrophysiological studies

Repeated administration of milnacipran for at least 7 days has been found, using electrophysiological techniques, to significantly attenuate the potency of 5-HT to inhibit the firing of serotonergic neurons in the raphe nucleus while inhibition of the CA1 field potential by 5-HT in the hippocampus is not modified (Mochizuki et al 2002b). This suggests that milnacipran rapidly desensitizes presynaptic somatodendritic 5-HT_{1A} receptors but not postsynaptic 5-HT_{1A} receptors.

Similar studies on the noradrenergic system found that milnacipran hyperpolarizes locus coeruleus neurons and enhances the inhibitory postsynaptic potential by increasing endogenous NE at synapses within locus coeruleus (Kuwahata et al 2004).

Methylphenidate, which is used in the treatment of attention deficit/hyperactivity disorder (ADHD), is thought to act as an indirect NE and DA receptor agonist. The electrophysiological effects of methylphenidate and milnacipran have been compared (Kidani et al 2005). Both compounds produced a concentration-dependent hyperpolarizing response in locus coeruleus neurons, which blocked spontaneous firing of locus coeruleus neurons. The hyperpolarization was blocked by the α_2-adrenoceptor antagonist, yohimbine, suggesting that it is mediated by NE acting on α_2-adrenoceptors on locus coeruleus neurons. The similar results obtained with methylphenidate and milnacipran suggest that the antidepressant may be helpful in the treatment of attention deficit hyperactivity disorder. This hypothesis has yet to be tested clinically.

TCAs are known to inhibit various ligand-gated ion-channel (LGIC) receptors, and some of their clinical features may be associated with this activity. Ueta et al (2004) investigated whether this might also be the case with milnacipran. The two-voltage clamp technique was used to measure the in vitro effects of milnacipran on the activity on four recombinant LGIC receptors, nicotinic acetylcholine, N-methyl-D-aspartate, gamma-amino butyric acid (GABA), and 5-HT_{3A} receptors expressed in Xenopus oocytes. Milnacipran showed no interaction at the GABA receptor

while the three other LGIC receptors were only inhibited by very high concentrations of milnacipran suggesting that, unlike the TCAs, under clinical conditions milnacipran has no significant effects on these receptors.

Effects on brain plasticity

Changes in brain plasticity involve neuronal atrophy, neurogenesis, dendrite involution and formation, and long-term potentiation (LTP), which is a form of synaptic plasticity that is thought to underlie learning and memory. These changes have been suggested to play a major role in the neurobiological basis of depression (Reid and Stewart 2001). Several studies carried out by Japanese researchers have investigated the role of milnacipran in changes in brain plasticity.

A single administration of milnacipran suppresses LTP in the hippocampal CA1 field in rats (Tachibana et al 2004), an effect which was reversed by pretreatment with the selective 5-HT_{1A} receptor antagonist, WAY 100635, or the α_1-adrenoceptor antagonist, prazosin, but not the α_2-adrenoceptor antagonist, idazoxan. Repeated treatment with milnacipran for 14 days, however, completely restored the suppression of LTP caused by single milnacipran treatment (Tachibana et al 2006). In addition, LTP suppression induced by the 5-HT_{1A} receptor agonist, tandospirone, was also completely reversed by repeated treatment with milnacipran.

In a conditioned fear stress paradigm, rats that received foot-shock stimulation every day for 5 days were found, 10 days later, to have increased freezing behavior. Electrophysiological studies in rats subjected to the same paradigm were found, after 10 days, to have suppressed LTP in the CA1 field of the hippocampus. Chronic but not acute treatment with milnacipran reduced both freezing behavior and the suppressed LTP induced by conditioned fear stress (Matsumoto et al 2005).

Thus repeated administration of milnacipran is capable of restoring LTP suppressed by both drugs and behavioral techniques. Single and repeated administration of milnacipran increase extracellular NE in the hippocampus to a similar extent whereas the increased extracellular 5-HT resulting from a single administration of milnacipran is further enhanced by repeated treatment. This suggests that milnacipran-induced restoration of LTP following repeated exposure may be the result of enhanced 5-HT neurotransmission (Tachibana et al 2006) rather than effect on the noradrenergic system.

Increasingly LTP is seen as a means of protection against the negative effects of stress and its restoration may be a common down-stream function in the treatment of disorders such as depression (Cooke and Bliss 2005).

Effects on the hypothalamic–pituitary–adrenal axis

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis is widely considered to be implicated in the pathophysiology of depression. Antidepressant drugs have been suggested to exert their clinical action via a facilitation of glucocorticoid receptor gene expression and function in the HPA (Brady et al 1991). Milnacipran, in common with other antidepressants such as desipramine, clomipramine, fluoxetine and clorgyline, has been shown to induce a rapid and sustained translocation of the glucocorticoid receptor into the nucleus of human lymphocytes in vitro (Okuyama-Tamura et al 2003).

Effects in animal behavioral models

Animal behavioral models for depression and anxiety can be useful in orientating clinical research. Japanese studies (Mochizuki et al 2002a) have confirmed the effects of milnacipran in behavioral studies carried out in Europe (reviewed in Briley et al 1996). Milnacipran significantly reduced the duration of both the immobility time in the forced swimming test (depression test) and the freezing time in the conditioned fear stress test (anxiety test) in rats.

Conditioned fear stress (CFS)-induced freezing behavior has been proposed as an animal model of anxiety especially social anxiety. CFS-induced freezing is attenuated by the acute administration of milnacipran as well as the SSRIs, citalopram and fluvoxamine, whereas the selective NE reuptake inhibitor, maprotiline, was inactive (Hashimoto et al 1996). These results suggest an important role for the facilitation of 5-HT neurotransmission in the reduction of CFS-induced freezing behavior. A study in an analogous model in mice showed similar results with milnacipran and fluvoxamine inhibiting conditioned fear stress induced freezing behavior to a similar extent (Miyamoto et al 2004).

The clinical efficacy of fluvoxamine in social anxiety disorder has been demonstrated by placebo controlled trials in the USA (Stein et al 1999), Europe (Westenberg et al 2004) and Japan (Asakura et al 2006). In addition, results from open studies suggest that both milnacipran (Nagata et al 2003, 2005) and fluvoxamine (Matsunaga et al 2001) may be active in the treatment of Taijin Kyofusho: a specific Japanese form of social anxiety disorder (see below). Milnacipran is thus likely to be useful in the treatment of social anxiety disorder.

Milnacipran has been tested in a number of animal models of chronic pain (Mochizuki 2004). In a model of chronic pain based on the injection of formalin into the paw of a rodent, milnacipran and inhibitors of NE reuptake, such as nisoxetine, nortriptyline and maprotiline, produced potent anti-nociceptive effects, whereas SSRIs, such as fluvoxamine, were much less potent. Another model involving ligation of the 5th spinal nerve induces behavioral signs in rats and mice that are similar to the symptoms of human neuropathic pain. In this model, the TCAs amitriptyline, a relatively non-selective 5-HT and NE reuptake blocker, and desipramine, a preferential NE reuptake inhibitor, and the SNRIs milnacipran and duloxetine, all significantly decreased sensitivity to pain. The SSRI, fluoxetine, however, was ineffective (Mochizuki 2004).

Using a rat model of neuropathic pain involving ligation of the left L5 and L6 spinal nerves, Obata et al (2005) showed that milnacipran injected directly into the spinal cord produced dose-dependent reduction in pain sensitivity which lasted for 7 hours. The intrathecal administration of paroxetine or maprotiline did not modify pain sensitivity. The reduction in pain sensitivity produced by milnacipran was attenuated by intrathecal co-administration of the α_2-adrenoceptor antagonist, yohimbine, or the 5-HT receptor antagonist, methysergide. These results suggest that antidepressants acting on both the noradrenergic and serotonergic systems are more effective than those acting on a single neurotransmitter system.

These positive findings in animal models of chronic pain have stimulated considerable clinical interest and milnacipran has now been tested in a number of clinical situations of chronic pain (see below).

Human pharmacokinetics

Genetic polymorphisms of cytochrome P450 metabolic enzymes can have profound effects on the efficacy and tolerance of drugs (see for example Mamiya et al 1998). Studies with Japanese human liver and intestinal microsomes (Tsuruta et al 2000) have shown that milnacipran does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 at clinically relevant concentrations. Phase I studies in Japan (unpublished) have shown that milnacipran is mainly excreted unchanged in urine, partly as a glucuronide conjugate and partly unchanged. The drug is only metabolized to a limited degree (less than 20%), principally to an inactive metabolite, N-desmethyl-milnacipran, by the action of CYP3A4 in the liver. These results are the same as those obtained in Europe (Puozzo and Leonard 1996) indicating that there is no reason to expect any racial differences in the properties of milnacipran based on differences in its pharmacokinetic characteristics.

Clinical studies

Double-blind randomized clinical trials in Japan

Early Japanese clinical experience with milnacipran has been reviewed previously (Mimura 2001; Tajima 2002). There have been few randomized clinical trials carried out in Japan. One of the first was a double-blind, parallel-group trial comparing treatment with milnacipran and imipramine (Yamashita et al 1995) in 127 depressed patients. The patient population was comparable to that included in the European comparative studies (Kasper et al 1996). Treatment with both imipramine and milnacipran was started at 50 mg/d (25 mg twice daily) for the first week and then increased flexibly up to a maximum of 150 mg/d. Mean final dose administered was 77 mg/d for milnacipran and 89 mg/d for imipramine. Depressive symptoms improved progressively in both groups. After the first week significantly more patients (53.2%) in the milnacipran group were considered to be "moderately" or "substantially" improved compared to those in the imipramine group (18.8%) ($p = 0.029$). At the end of the study, however, there was no significant difference between treatments with 58% of patients in the milnacipran group and 56% in the imipramine group considered "moderately" or "substantially" improved.

Another double-blind, parallel-group study compared milnacipran and mianserin in 178 patients (Endo et al 1995). Patients received either milnacipran 50 mg/d (25 mg twice daily) or mianserin 30 mg/d (15 mg twice daily) for the first week. The dose could then be increased to a maximum of 100 mg/d milnacipran or 60 mg/d mianserin. The mean final doses of milnacipran and mianserin were 75 mg/d and 43 mg/d, respectively. At the end of the 4-week treatment period, 40% and 37% of patients were considered to be "moderately" or "substantially" improved in the milnacipran and mianserin treatment groups respectively. There was no significant difference between treatments.

These studies show the non-inferiority of the antidepressant efficacy of milnacipran as compared to the principal reference antidepressants used in Japan at that time.

The adverse events reported for milnacipran in the comparative study with imipramine in Japan were similar

in nature and frequency to those seen in European studies (Kasper et al 1996). Interestingly, the adverse events profile seen with milnacipran in the imipramine study differed considerably from that seen in the mianserin study (Table 1). For example, dry mouth and constipation were much more frequent with milnacipran in the imipramine study than in the mianserin study, whilst the opposite was true for drowsiness. Dry mouth and drowsiness are known and expected side-effects of imipramine and mianserin respectively. Expected side-effects were probably sought more conscientiously, and may have thus been over-represented in the milnacipran groups in these studies. This shows the importance of comparing side-effect data only within a similar context since the nature of the comparator drug can have a considerable influence on the adverse effects reported for a new investigational drug.

These two phase III trials in Japanese patients suggest that milnacipran has comparable efficacy in Japan to that seen in European studies. In both areas milnacipran was shown to be as effective as traditional reference antidepressants in the treatment of depression. Tolerance of milnacipran also appears similar in Japan and Europe in spite of the popular belief that Japanese patients are more sensitive to adverse effects.

Investigative clinical studies with milnacipran in Japan

Formal randomized double-blind controlled trials are atypical in Japan and there have been very many more investigative clinical studies carried out with milnacipran usually at the initiative of the investigators. Although many of these studies have methodological limitations they have the merit of asking questions and suggesting answers outside of the context limited by regulatory preoccupations.

Predicting antidepressant response with milnacipran

As with all antidepressants, some patients respond better to milnacipran than others. Several studies have tried to throw light on factors which may help identify probable responders.

In a group of 80 patients treated for 6 weeks with milnacipran, a study found that certain polymorphisms of the NE transporter genes were related to differences in response rates (Yoshida et al 2004a). The presence of the T allele of the NET T-182C polymorphism was significantly ($p = 0.03$) correlated with a greater response with milnacipran, whereas the A/A genotype of the NET G1287A polymorphism was associated with a slower onset of response. In contrast, the presence of the 5-HT transporter gene polymorphisms, 5HTTLPR and 5HTTVNTR, had no effect on the antidepressant response to milnacipran.

Another study (Shinkai et al 2004) found that responders to milnacipran had significantly *lower* pretreatment levels of plasma 3-methoxy-4-hydroxyphenylglycol (pMHPG) compared to non-responders ($p = 0.023$). In addition, improvement in depressive symptoms over 4 weeks, as measured by the Hamilton Depression Rating Scale (HAMD), was significantly correlated with increases in pMHPG levels ($p = 0.03$). Responders to paroxetine, on the other hand, had significantly *higher* pretreatment levels of pMHPG compared to non-responders ($p = 0.001$) with a negative correlation between changes in pMHPG levels and improvement of the HAMD. This suggests that milnacipran act primarily on the noradrenergic system in contrast to paroxetine which acts primarily on the serotonergic system.

A case-control comparison of milnacipran and fluvoxamine in 202 outpatients with major depression found that the overall response rates were similar for both antidepressants. In more severely depressed patients ($HAMD_{17} > 19$), however, there were significantly more responders (≥50% reduction in $HAMD_{17}$ baseline score) with milnacipran (68.9%) than with fluvoxamine (46.2%) ($p = 0.046$) (Fukuchi and Kanemoto 2002). In addition patients with high scores on the "agitation" and "insomnia" items of the HAMD were more likely to respond to milnacipran than to

Table 1 Comparison of principal adverse events reported in European and Japanese comparative studies of milnacipran vs imipramine and milnacipran vs mianserin

	European study		Japanese studies			
	Milnacipran	**Imipramine**	**Milnacipran**	**Imipramine**	**Milnacipran**	**Mianserin**
Dry mouth	17%	36%	21%	31%	6%	13%
Constipation	13%	21%	7%	14%	2%	8%
Nausea	7%	4%	7%	2%	6%	1%
Dizziness	5%	9%	7%	14%	2%	6%
Drowsiness	3%	6%	5%	5%	6%	32%

Compiled from data in Tignol et al (1998), Yamishita et al (1995), and Endo et al (1995).

fluvoxamine. These results are similar to those found in a double-blind study carried out in Europe in moderately to severely depressed (mean $HAMD_{24}$ = 32.2) patients (Clerc et al 2001) which concluded a superior efficacy of milnacipran over fluvoxamine.

In another study, 80 Japanese patients with major depressive disorders were stratified by severity according to their baseline Montgomery-Asberg Depression Rating Score (MADRS): "severe" MADRS ≥31 (n = 25); "moderate" MADRS = 25–30 (n = 30) and "mild" MADRS = 21–24 (n = 25) (Sugawara et al 2006). "Severe" and "moderate" patients had more melancholia than "mild" patients (17, 6, and 1 patient respectively). Milnacipran was administered twice daily for 6 weeks at an initial dose of 50 mg/d for the first week and then 100 mg/d. Mean plasma levels of milnacipran were similar in the "severe" and "mild" groups but significantly higher in the "moderate" group. The response rates were 72%, 70%, and 44% in the "severe," "moderate," and "mild," categories respectively (Figure 1). The differences between "severe" and "mild" and "moderate" and "mild" were significant whereas the difference between severe and moderate was not. This study suggests that milnacipran may be more effective in treating patients with moderate and severe major depression compared to those with mild depression.

A retrospective cohort analysis of 159 outpatients treated for depression in a Japanese hospital with fluvoxamine, paroxetine or milnacipran found that older patients (≥50 years) had a superior response rate with milnacipran than with the other antidepressants (Morishita and Arita 2004a). For patients under 50 years fluvoxamine was the most effective antidepressant.

There have been suggestions that female patients may respond more favorably than male patients to SSRIs whereas the opposite appears to be true for TCAs (Kornstein et al 2000). In a retrospective cohort analysis of 63 depressed patients (34 males, 29 females) treated with milnacipran, there was a tendency ($p < 0.1$) towards a higher frequency of improvement among males (83%) than females (62%) (Morishita and Arita 2003b). The percent responders was, however, significantly higher among both males and females with a first episode of depression than among those with a recurrent episode (Table 2).

Taken together the above studies suggest that depressed patients with deficient noradrenergic neurotransmission, as indicated by MHPG levels and norepinephrine transporter polymorphisms, respond particularly well to treatment with milnacipran. In addition patients with more severe depression, especially those with melancholia, appear to respond better to milnacipran than patients with mild depression. There are also suggestions for a better response to milnacipran among the elderly and in patients with their first episode of depression. These latter observations, however, need to be confirmed in larger cohorts.

Differences between doses of milnacipran

Although intuitively most clinicians assume that a dose-response relationship exists for antidepressants it has proven difficult to demonstrate this for TCAs (Bollini et al 1999) and for SSRIs (Baker et al 2003). Not only are the symptoms of depression variable in nature and in their pattern of improvement but the pharmacokinetics of many antidepressants are complicated by variable absorption, active metabolites, and genetic variation in metabolic enzymes. For determining the possible existence of a dose-efficacy relationship, milnacipran is close to being an "ideal" antidepressant, with an oral bioavailability close to 100%, low protein binding, very little metabolism, and an absence of active metabolites (Puozzo and Leonard 1996).

The relationship between antidepressant effects and plasma levels of milnacipran was investigated in 49 patients with major depression (Higuchi et al 2003). Patients were treated for 6 weeks with milnacipran at 50 mg/d for the first week and the flexibly up to 100 mg/d thereafter. Depressive symptoms were evaluated by the MADRS before treatment and after 1, 2, 4, and 6 weeks. Nearly 70% of patients responded (≥50% decrease in baseline MADRS) and the difference between responders and non-responders was significant from the first week of treatment. The mean plasma milnacipran level of responders (82.0 ± 29.4 ng/ml) and non-responders (78.6 ± 23.1 ng/ml) were not, however, significantly different. Furthermore no significant linear or curvilinear relationship was found between the final MADRS score and the plasma levels of milnacipran.

Table 2 Patients responding to milnacipran according to gender and frequency of episode

	Men	Women
Overall responders	82.4%[#]	62.1%
1st episode responders	100%[*]	85.7%[*]
Recurrent episode responders	56.3%	42.9%

Responders = decrease ≥50% in baseline HAMD.
[#]$p < 0.1$ compared with overall response rate in women.
[*]$p < 0.5$ compared with recurrent episode responders of the same sex.
Data from Morishita and Arita (2003a).

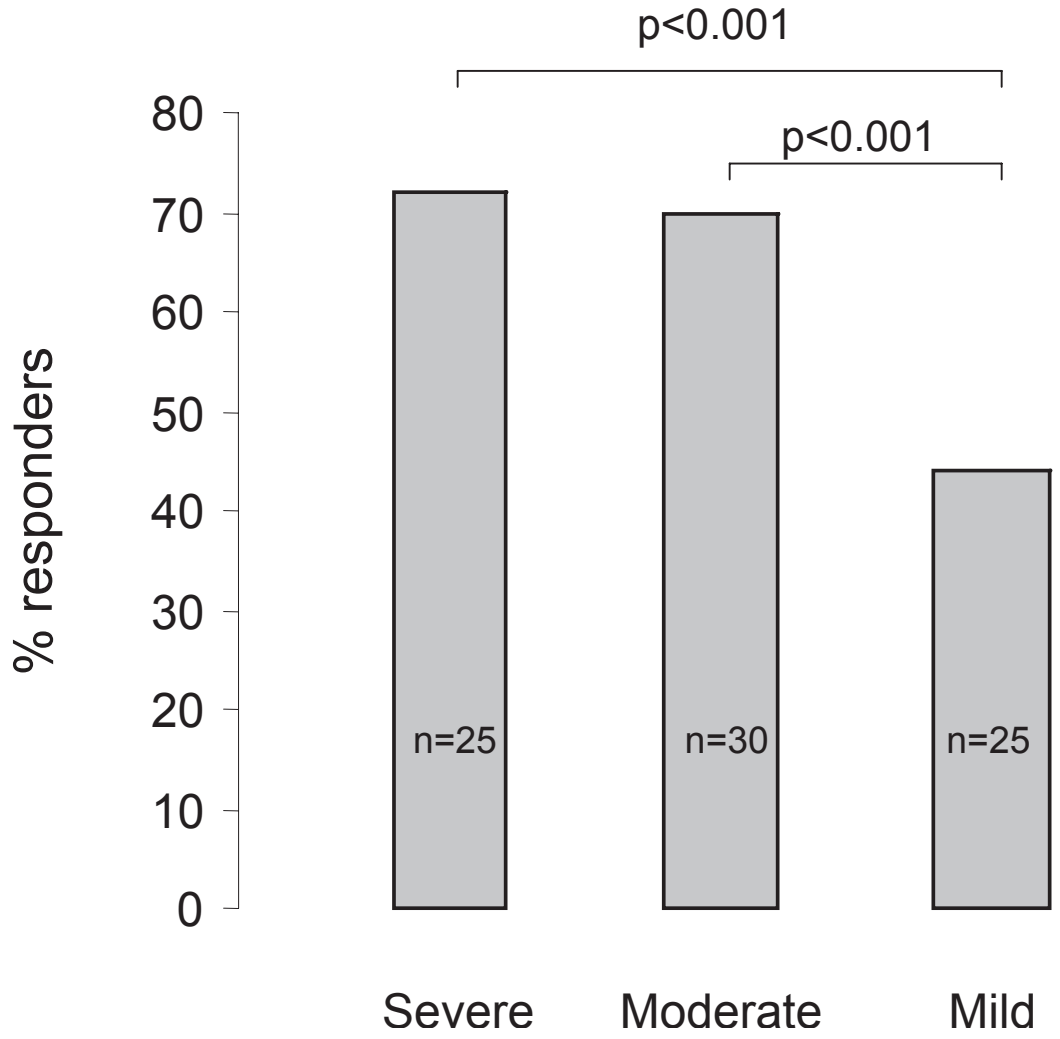

Figure 1 Response to milnacipran in patients stratified by severity. Severity was defined by baseline MADRS; Severe = MADRS ≥ 31; moderate = MADRS 25–30; mild = MADRS 21–24; Response = reduction ≥50% of the baseline MADRS; Drawn from data from Sugawara et al (2006).

Another study approached the question of dose-response relationship in a different way. The doses of 50 mg/d and 100 mg/d of milnacipran (both given twice daily) were compared in a group of 32 depressed patients. No significant difference was found in the percentage of responders at each dose after 8 weeks (Morishita and Arita 2003c). A difference in the onset of action was, however, observed. The cumulative percentage of responders in the 50 mg/d group reached 80% after 6 weeks, while in the 100 mg/d group this same level was reached two weeks earlier at 4 weeks. At the end of 3 weeks treatment there was a significantly greater cumulative percentage of responders in the higher dose group.

Two different doses of milnacipran (75 mg/d and 150 mg/d) were compared in 66 outpatients with major depression who were experiencing their first depressive episode or whose previous depressive episode had occurred at least 1 year earlier (Kanemoto et al 2004). Patients were randomized and titrated to a daily dose of milnacipran of either 75 mg or 150 mg over 2–3 weeks. This dose was then maintained stable for 8 weeks. At the end of the study the rates of both response (≥50% decrease in $HAMD_{17}$ from baseline) and remission ($HAMD_{17} < 7$) were significantly greater in patients receiving milnacipran at 150 mg/d compared with patients receiving milnacipran at 75 mg/d (Figure 2). There was no significant difference in the incidence of adverse events.

Thus in spite of the absence of a clear relationship between plasma levels and clinical response, there is considerable evidence to suggest an enhanced (or accelerated) response to milnacipran at higher doses.

Milnacipran in the treatment of different types of depression

The clinical trials that led to the registration of milnacipran in Japan, as in the rest of the world, were limited to patients with "pure" depression. Depression, however, is frequently co-morbid with other psychiatric and non-psychiatric disorders. Japanese curiosity has led to the experimentation of milnacipran in numerous populations of depressed patients with various co-morbid disorders or other particularities.

Bipolar depression

All antidepressants have the potential to induce mania (Preda et al 2001). Two studies (Table 3) have investigated the use of milnacipran in mania.

Although the data are limited these studies suggest that milnacipran is a safe option in the treatment of patients with bipolar depression with little on no tendency to induce mania.

Milnacipran in resistant depression

In clinical research resistant depression has a specific definition. In clinical practice, however, the term is often used to describe the depression in patients who have not obtained a satisfactory response from an antidepressant treatment. Used in this sense, the effect of milnacipran in resistant depression has been the subject of a small study in Japan (Table 3) which suggests that milnacipran can be useful in some patients resistant to other antidepressants. Full controlled trials are, however, required to confirm this point.

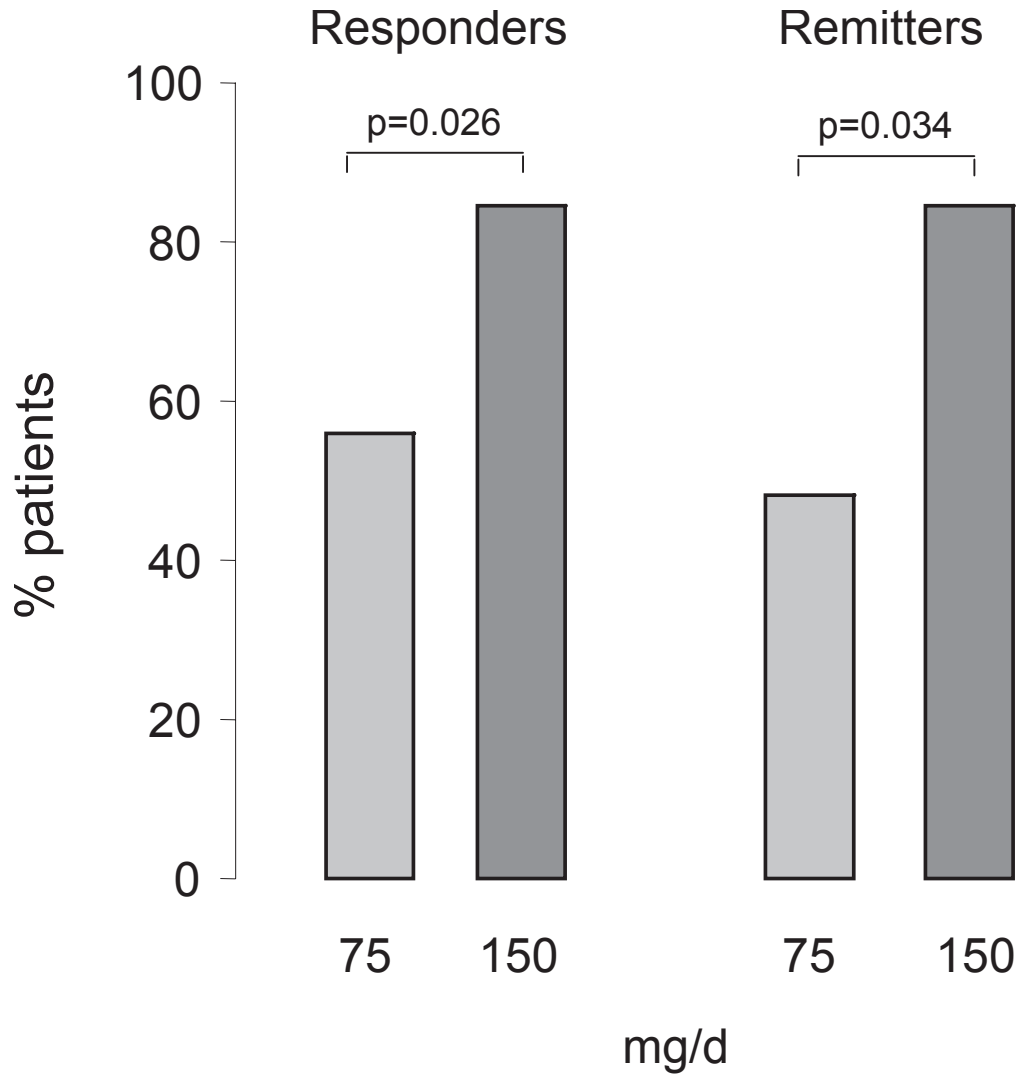

Figure 2 Response to milnacipran at different doses. 66 patients were randomized and titrated to a daily dose of milnacipran of either 75 mg or 150 mg over 2–3 weeks; This dose was then maintained stable for 8 weeks; 25 and 26 patients, respectively, completed the study in the 75 mg/d and 150 mg/d groups; Response = reduction ≥50% in $HAMD_{17}$ from baseline; Remission = $HAMD_{17}$ <7; Drawn from data from Kanemoto et al (2004).

Depression following brain trauma or stroke

Mild to moderate traumatic brain injury is often followed by depression (Alderfer et al 2005). Depression is also common after stroke and has numerous similarities with depression following brain trauma (Gupta et al 2002). Studies with TCAs and SSRIs have suggested that an antidepressant with a noradrenergic component is required for the best efficacy in this condition. Nortriptyline, for example, has been shown to be superior to the SSRI fluoxetine in a large double-blind, placebo-controlled trial (Robinson et al 2000). Studies with milnacipran in post-trauma and post-stroke depression (Table 3) suggest that milnacipran may be particularly effective. One study which measured cognitive impairment (Table 3) found that milnacipran produced a significantly greater improvement than no treatment. Thus milnacipran may be effective in relieving the depression often associated with brain trauma or stroke without any negative impact on functional recovery. Unfortunately, however, the antidepressant does not appear to accelerate rehabilitation.

Depression in Parkinson's disease

Depression is frequently co-morbid with Parkinson's disease with anhedonia and apathy as the principal symptoms (Okun and Watts 2002). Both TCAs and SSRIs have been used to treat depression associated with Parkinson's disease. The poor tolerance of the TCAs and the tendency of SSRI to worsen motor function have stimulated the search for other therapeutic options (Richard and Kurlan 1997). Some studies have found that compounds stimulating principally noradrenergic neurotransmission are better able to improve depression in parkinsonian patients (Andersen et al 1980; Narabayashi et al 1991).

A pilot study (Table 3) showed a reduction in depressive symptoms, especially anhedonia and apathy with milnacipran.

In addition, two cases have been reported (Takahashi et al 2005) of parkinsonian patients with depression with an insufficient antidepressant response to SSRIs who were switched to milnacipran and achieved complete remission.

These cases suggest that milnacipran is a potentially useful treatment of depression in patients with Parkinson's disease, which is well tolerated and has no adverse effects on motor function and does not interact pharmacokinetically with parkinsonian treatment. There is a suggestion that it may usefully replace SSRI treatment where this does not lead to full remission.

Depression in schizophrenia

Over 25% of schizophrenic patients manifest depressive symptoms (Siris 1991), which predict a poor overall outcome of treatment. Because of its lack of potential for drug interaction (Puozzo and Leonard 1996), milnacipran has an advantage in treating depressive symptoms in schizophrenic patients already receiving antipsychotic medication. A pilot study in 7 schizophrenic patients with depressive symptoms (Table 3) showed a marked response in some patients but no response in others. Milnacipran was well tolerated and none of the patients had any aggravation of their psychotic symptoms.

Depression in Alzheimer's disease

The prevalence of depression in Alzheimer's disease patients varies from 5% to nearly 45% depending on the criteria used (Vilalta-Franch et al 2006). The results of a pilot study (Table 3) result suggest that milnacipran may be a potentially useful treatment of depression in patients with Alzheimer's disease. In addition since Alzheimer's patients are frequently polymedicated, milnacipran's low potential for drug–drug interactions is another advantage in this patient population.

Depression induced by treatment with interferon

Interferons are important antiviral and neoplastic agents but one of the inconveniences of interferon therapy is the depression that they induce in certain patients (Trask et al 2000). Direct intracebroventricular injection of interferon-α in rats has been shown to cause a dose-related decrease in the levels of both 5-HT and NE (Kamata et al 2000) in the frontal cortex, which suggests that milnacipran could be effective in relieving interferon-induced depression. A case report of the use of milnacipran (Table 3) showed the total reversal of interferon-induced depression after 4 weeks of treatment.

Menopausal depression and premenstrual dysphoric disorder

The onset of menopause is often accompanied by a depressive state in women, although the mechanism involved is poorly understood. Premenstrual dysphoric disorder (PMDD), which has an estimated prevalence of 2%–9% in menstruating women (Yonkers 1997) is usually treated with SSRIs. Certain women, however, are intolerant of the digestive side-effects of these drugs and alternatives are frequently sought.

The duration of immobility of male rodents during the forced swimming test is a well known measure of a depression-like state. In a proposed model of menopausal depression, the duration of immobility was significantly increased in female mice following bilateral ovariectomy (Bekku and Yoshimura

Table 3 Effect of milnacipran in the treatment of different types of depression

Bipolar depression	Retrospective cohort analysis of depressed (uni or bipolar) patients	Paroxetine n = 79 ~12% bipolar Induction of hypomania 7/79 (8.9%)	Milnacipran n = 68 ~12% bipolar Induction of hypomania 1/68 (1.5%)	Morishita and Arita (2004b)
	Pilot study in 9 bipolar depressed	Milnacipran + pre-existing treatments (lithium, clonazepam, valproate or carbamazepine) 8/9 Efficacy without manic activation Prolongation of asymptomatic period in 6 rapid cycling patients		Yamada 2001a
Resistant depression	8 depressed females resistant to antidepressants (doses equivalent to 150 mg/d imipramine) administered from 4 to 17 months	Milnacipran as add-on therapy (30–100 mg/d) 1/8 drop-out (adverse effects)7/8 successful response (mood and psychomotor retardation most notably improved)		Yamada 2001b
Depression following brain trauma	6-week open pilot study in 10 patients with depression occurring following brain trauma	Milnacipran (30–50 mg/d) 1/10 drop-out (non-serious side-effects) 6/10 responders 4/10 remissions In all patients: improvement in cognitive function		Kanetani et al 2003
Post-stroke depression	12 patients with major or minor depression (onset subsequent to a cerebral infarction or hemorrhage)	Milnacipran (60–50 mg/d) for 6 weeks 2/12 dropped out 3/12 experienced non-serious side-effects but continued the study 7/12 remitted		Kimura et al 2002
	18 patients with depression occurring within 3 months of a stroke. Open comparison	Milnacipran 30–60 mg/day (n = 10) Antidepressant treatment refusal (n = 8) Improvement in cognitive function (MMSE score) Milnacipran > no treatment (p = 0.034). No difference between the two groups for changes in depression.		Sato et al 2006
	11 patients in a rehabilitation hospital compared to untreated controls	Milnacipran given for 3 months Greater improvement of depression (Zung) in milnacipran group but similar rehabilitation in both groups		Yamakawa et al 2005
Depression in Parkinson's disease	12-week pilot study in 8 patients	Milnacipran (30–60 mg/d) 1/8 patient withdrew (palpitations and agitation) 7/8 patients reduced depressive symptoms (especially anhedonia and apathy) from week 4		Maruyama 2003
Depression in schizophrenia	7 schizophrenic patients with depressive symptoms	Milnacipran in addition to both traditional and atypical antipsychotics Depressive symptoms 3/7 marked improvement 1/7 slight improvement 3/7 unchanged		Nakanishi et al 2004
	55-year-old woman with delusional depression with anorexia	Milnacipran + olanzapine Resolution of all symptoms		Sugawara et al 2005
Depression in Alzheimer's disease	Open-labeled study in 11 Alzheimer's patients with major depressive symptoms	Milnacipran Within 12 weeks 10/11 responders 8/11 sustained remissions with considerable improvement in global functioning		Mizukami et al 2006

(Continued...)

Table 3 *Continued*

		2/11 mild hypomania 1/11 daytime somnolence (problems resolved after reducing the daily dose of milnacipran) No negative effects on cognitive function.	
Depression induced by treatment with interferon	A 71-year-old man with cancer, treated by interferon-α2A, complained of depressed mood, lassitude and irritability.	No relief of depressive symptoms with reduction of interferon dose Only partial efficacy with trazodone Progressive replacement of trazodone by milnacipran Decline of depressive symptoms. After 4 weeks milnacipran treatment, disappearance of symptoms with no resurgence after interferon injections.	Yoshida et al 2003
Depression in cancer patients	A terminally ill cancer patient with major depressive disorder	Milnacipran Rapid improvement in symptoms after 1–2 weeks.	Sato et al 2004
Menopausal depression and premenstrual dysphoric disorder (PMDD)	3 women with PMDD not tolerating SSRI treatment	Milnacipran at 30 mg/d (15 mg twice daily) in the luteal phase 2/3 improved 1/3 improved when dose increased to 60 mg/d (30 mg twice daily)	Yamada and Kanba 2005

2005). Chronic treatment with estradiol prevented this increased immobility. Chronic treatment with milnacipran as well as imipramine and fluvoxamine significantly reduced the duration of the immobility. These results suggest that the forced swim test in ovariectomized female mice may be a useful animal model for menopausal depression and that milnacipran is likely to be as effective in this type of depression as the TCAs or the SSRIs.

Clinical support of this suggestion has come from the successful treatment of PMDD by milnacipran of 3 women who could not tolerate SSRI treatment (Table 3).

Boosting the action of milnacipran

Low energy, lack of motivation and fatigue are residual symptoms often seen in patients with only a partial response to antidepressants (Nierenberg and DeCecco 2001). The biological basis of these symptoms in depression is unclear but some reports suggest that a persistent decrease in brain NE and dopamine may be involved (Schmidt et al 2001). A treatment that enhances neurotransmission of these two monoamines is likely to boost energy and reduce fatigue in patients with these symptoms of depression. Two cases have been reported of the successful combined use of milnacipran and the dopamine agonist, cabergoline, to achieve complete remission in patients whose residual symptoms, including energy loss and fatigue, were refractory to previous treatments (Takahashi et al 2003). In both cases treatment with SSRIs achieved only limited response. Switching to milnacipran produced greater response but not complete remission with low energy, lack of motivation and fatigue remaining as the principal residual symptoms. Supplementation with lithium or thyroid hormone was without effect. The addition, however, of the dopamine receptor agonist, cabergoline, achieved full sustained remission in both cases.

Lithium is a standard augmentation therapy for antidepressants (see for example Moret 2005). The administration of lithium to rats significantly increased basal levels of extracellular 5-HT in the medial prefrontal cortex (Kitaichi et al 2005b). Milnacipran combined with lithium treatment resulted in a greater increase in extracellular 5-HT, as well as increases in the levels of NE and dopamine which were greater than with milnacipran alone (Kitaichi et al 2005b). This suggests that lithium augmentation might increase the antidepressant effect of milnacipran while respecting the balance of effects on the monoamines.

A pilot study using the treatment algorithm established by the Japanese Psychopharmacology Algorithm Project (JPAP) (Kobayashi et al 2004) found that the combination of lithium with milnacipran was the most effective second-line therapy with 4 out of 4 patients responding to a combination of milnacipran and lithium after failure of a first-line therapy with a SSRI. Although more cases need to be investigated, the

combination of lithium and milnacipran should be considered a potentially useful second-line therapy.

Typically antidepressants take at least 4 weeks to provide significant benefit. An open pilot study of 21 depressed patients tested the effect of co-administering the SSRI, fluvoxamine, with milnacipran. The cumulative percentage of responders reached over 80% within 3 weeks with the combined treatment (Morishita and Arita 2005a). There were no patients under monotherapy for comparison in this study but an earlier retrospective cohort analysis of 206 out-patients found that the cumulative percentage of responders receiving milnacipran alone reached 80% within 4 weeks, whereas for patients treated with fluvoxamine or paroxetine it took 6 weeks to achieve this same cumulative percentage of responders (Morishita and Arita 2003a). This study suggests that a more rapid onset of action may possibly be achieved by the use of a combination of antidepressants with different mechanisms of action. A replication is obviously necessary.

Five patients with major depression without psychotic features who responded only partially to milnacipran alone, even at doses of up to 300 mg/d, were co-administered the atypical antipsychotic, risperidone (usually at 1 mg/d) (Tani et al 2004). Rapid improvements of depressive symptoms occurred within 1–4 days. In all cases the patients subsequently achieved full remission on the combination therapy.

Milnacipran in disorders other than depression

Anxiety

Most antidepressants have been found to be active in a number of disorders in addition to depression. The SSRIs have been the most investigated in this respect and it is generally accepted that most (if not all) SSRIs are effective in the whole spectrum of anxiety disorders (Vaswani et al 2003). The SNRI venlafaxine has also been extensively studied in anxiety (Silverstone 2004; Stahl et al 2005).

A small open study of 12 patients investigated the efficacy of milnacipran in generalized anxiety disorder (Tsukamoto et al 2004). Two patients discontinued because of adverse effects (nausea). All 10 of the patients completing the study were markedly improved with a reduction of their Hamilton anxiety (HAMA) scores of at least 70% over the 8-week study.

Taijin-Kyofusho (TKS) is a distinct form of social anxiety disorder specific to Japanese culture in which patients suffer from intense fear that his or her body or its functions are offensive to other people. A 12-week open trial examined the effect of milnacipran in 12 patients with TKS with social anxiety disorder (Nagata et al 2003). Six of the 11 patients who completed therapy responded ("much improved" or "very much improved" on the Clinical Global Impression (CGI)—Improvement scale). The mean Liebowitz Social Anxiety Scale (LSAS) score and TKS offensive anxiety also showed statistically significant reductions.

In a follow-up study 16 patients with TKS were treated with milnacipran for 12 weeks (Nagata et al 2005). Six patients discontinued in the first few days of treatment because of nausea. Of the 10 who completed the study 7 responded (≤2 on the CGI-severity scale at endpoint). TKS offensive anxiety (fear of offending other people), which was assessed by an original scale developed by the authors, was significantly reduced. In addition patients' insight and emotional coping strategies were significantly improved. Although confirmation from placebo controlled trials is still lacking, these studies suggest that milnacipran may be helpful in treating this specific type of social anxiety.

Pain

TCAs are the antidepressants most commonly used in the treatment of chronic pain. The effect of these antidepressants on both NE and 5-HT is thought to be a key factor in their effect on chronic pain (Barkin and Fawcett, 2001) since SSRIs are not particularly helpful (Briley 2004). SNRIs such as milnacipran that can be seen as "well-tolerated TCAs" are thus an obvious therapeutic option to test in chronic pain.

Glossodynia is an orolingual chronic pain syndrome, which is characterized by a spontaneous burning sensation mainly affecting the tongue with clinically normal oral mucosa. Eleven patients with glossodynia and no history of significant psychiatric illness were treated with milnacipran on an open, variable dose, basis for 6 weeks (mean final dose 58.6 mg/d). Ten patients completed the study. Eight of these reported decreased pain intensity, 6 had a decrease of more than 50%, and 4 reported negligible pain at the end of the study. For most patients the maximal benefit was achieved within the first week of treatment (Toyofuku 2003). Another case, reported by Kamata et al (2003), was a 72-year-old housewife who suffered from glossal pain for 32 months although no tongue, nose, or throat abnormality was found. No depressive symptoms were noted. Non-steroidal anti-inflammatory drugs and diazepam were tried without success. These treatments were stopped and the patient was started on milnacipran at 50 mg/d. The pain subsided markedly

within 2 weeks and after a month the patient was virtually pain-free.

There have been a number of case reports of successful treatment of different types of chronic pain with milnacipran. Two cases of post-herpetic neuralgia improved with milnacipran have been independently reported (Shimamoto et al 2002; Utsunomiya et al 2002). In another case in a patient without depressive symptoms, milnacipran brought about a drastic improvement in refractory severe chronic pain in the left lateral femoral region whose severity the patient evaluated, on a VAS scale, at 94% (Kito et al 2005).

A fuzzy logic analysis of the verbal expression of pain into "surface" and "deep" pain (Morishita and Arita 2005b) was used to study a series of 5 patients with depression with painful symptoms. The authors found that the pain associated with depression was "deep" pain and that milnacipran was effective in relieving this "deep" pain in all of these patients.

Pain arising from orthopedic causes including osteoarthritis has also been successfully treated with milnacipran. A series of 15 patients with a primary diagnosis of orthopedic pain, including degenerative spondylosis, lumbar spinal canal stenosis and osteoarthritis of the knee with symptoms which included low back pain, ischialgia, intermittent claudication and lower limb arthralgia were administered milnacipran, at 50 mg/d, for 8 weeks. Twelve of the 15 patients completed the study. Of these, symptomatic improvement was seen in ten patients while in four patients pain was reduced by more than 80%. Symptoms remained unchanged in the other two patients (Tanikawa 2002).

A 39-year-old woman suffering from an extremely painful temporomandibular disorder which developed into a generalized fibromyalgia was treated with milnacipran, at a dose of 30 mg/d increasing progressively over 6 months to 120 mg/d. Dose and time-dependent improvements were observed in occlusal discomfort, generalized pain and the associated symptoms of sleep disorder, chronic fatigue, stiffness, numbness, and depressed mood. The treatment enabled the rehabilitation of the patient with a major improvement in her quality of life (Toyofuku and Miyako 2004).

An open-label clinical trial has also shown milnacipran to be effective in relieving pain and other symptoms in patients with fibromyalgia syndrome with co-morbid depressive symptoms (Nagaoka et al 2004). The efficacy of milnacipran in fibromyalgia has subsequently been confirmed in a double-blind placebo-controlled trial in the USA (Gendreau et al 2005).

Treatment of 5 non-depressed outpatients, who had been suffering from chronic pain for at least 3 months, with milnacipran has been reported by Kamata et al (2004). Chronic pain was assessed using a 100 mm visual analog scale (VAS) before and 12 weeks after the start of the milnacipran treatment or at the time the drug was stopped. The mean duration of pain before treatment was 17.8 months and the mean baseline pain intensity on the VAS was 88.2%. Milnacipran treatment was started at 50 mg/d and increased flexibly to 150 mg/d. The mean dose at the end of treatment was 85.0 mg/d. At the end of the treatment the mean pain intensity on the VAS was 61.2%. Three of the 5 patients showed marked improvement (decrease in VAS > 75%). One patient showed moderate improvement (42.0% decrease in VAS). The fifth patient experienced nausea and discontinued treatment after 4 weeks at which time his VAS had decreased by 14.3%.

Although most of the data come from case reports and small open studies, there is an accumulating mass of data to suggest that milnacipran may be helpful in the treatment of chronic pain both associated with and independent of depression (Briley 2004). In particular the confirmation, in a placebo-controlled trial, of efficacy of milnacipran in fibromyalgia (Gendreau et al 2005) should encourage the follow up of many of these studies by larger and more rigorously designed trials.

Memory

A single report has suggested that milnacipran may be useful in certain syndromes involving memory dysfunction such as Korsakoff's syndrome, a chronic memory disorder with both retrograde and anterograde amnesia. Noradrenergic, serotonergic, and cholinergic dysfunctions have been suggested to be involved in this syndrome (McEntee and Mair 1990).

A single case of memory improvement following treatment with milnacipran of a patient with Korsakoff's syndrome has been reported (Numata et al 2005). A 48-year-old woman was diagnosed with non-alcoholic Korsakoff's syndrome following herpes simplex encephalitis. Carbamazepine was administered for emotional instability and inappropriate behavior and resulted in a dramatic improvement of these symptoms but had no effect on her memory. Milnacipran (50–100 mg/d) was prescribed in addition to carbamazepine to improve memory disturbances. After 1 month of milnacipran treatment, memory performance, as measured with the Hasegawa dementia scale and the Benton visual retention test,

Table 4 Case reports from Japan describing unusual adverse events with milnacipran

Principal adverse event		Dose of milnacipran	Reversability upon stopping milnacipran	
Cold feet (cyanosis)	37-year-old male	100 mg/day	Full reversal	Kamata & Higuchi 2005
Hypertension (150/100 mm Hg without subjective symptoms)	53-year-old male	450 mg/day	Dose-dependent reversal	Yoshida et al 2002
Ejaculation after defecation without orgasm	31-year-old male	100 mg/day	Full reversal	Yoshida et al 2004
Parkinsonism	83-year-old female	30 mg/day	Important reversal but some minor symptoms remained 4 weeks after stopping	Aria 2003

were significantly improved permitting the patient to leave hospital. Further studies are clearly warranted in this area.

Tolerability

As already mentioned, the tolerability of milnacipran in Japanese patients is, in general, similar to that observed in Europe and other parts of the world. No "Japan-specific adverse events" have ever been reported. Considering the number of Japanese patients treated with milnacipran and the popularity of case reports in Japan there have been very few case reports of intolerability of milnacipran. The four published case reports brought to light by a Medline search carried out in July 2006 are summarized in Table 4.

The principal adverse effects seen with milnacipran in Japan, as in Europe, can be explained by the pharmacology of the mechanism of action of milnacipran, namely the potentiation of noradrenergic and serotonergic neurotransmission in the brain and the periphery. As such the adverse effects are invariably reversible and respond to dose reduction or withdrawal of the drug.

Conclusions

Well over half of the publications concerning milnacipran over the last 5 years have originated from Japan according to a Medline search. This is probably an underestimate since it excludes most publications in Japanese and many publications in minor Japanese journals that are not covered by Medline.

Although most of the clinical studies are small and many of them lack rigorous protocols, they have the merit of exploring many areas of potential interest for a new antidepressant drug including its use in patients with co-morbid disorders and disorders other than depression.

The studies reviewed here suggest that patients with serotonergic and, more importantly, noradrenergic deficits and those with more severe depressive symptoms are likely to respond best to milnacipran. Milnacipran is likely to be active in anxiety, especially generalized social anxiety. The probable activity in chronic pain disorders has already been confirmed by controlled studies in fibromyalgia.

As a well-tolerated antidepressant with a very low risk of drug–drug interactions, milnacipran would be expected to be useful in depressed patients with various co-morbid disorders. Numerous and varied reports from Japanese clinicians indeed suggest this.

Finally the very few case reports of adverse events that have been published confirm the good tolerability of milnacipran predicted by its preclinical profile and early clinical trials. There is no evidence of any differences in efficacy or adverse events between Japanese patients and those from other parts of the world. It would therefore appear legitimate to extrapolate from the Japanese experience to all other parts of the world.

Disclosures

TH has no conflict of interest. MB is a consultant for Pierre Fabre Médicament and Asahi Kasei Pharma.

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