

SNRIs: The Pharmacology, Clinical Efficacy, and Tolerability in Comparison with Other Classes of Antidepressants

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FOCUS POINTS

- Venlafaxine, milnacipran, and duloxetine block the reuptake of serotonin (5-HT) and norepinephrine (NE) with differing selectivity. Approximate potency ratios (5-HT:NE) are 1:1 for milnacipran, 1:10 for duloxetine, and 1:30 for venlafaxine.
- When used at doses that cause inhibition of the reuptake of both 5-HT and NE, treatment with all three serotonin and norepinephrine reuptake inhibitors (SNRIs) produce higher rates of response and remission from major depression than the selective serotonin reuptake inhibitors (SSRIs).
- SNRIs are effective in treating a variety of anxiety disorders. Efficacy of SNRIs and SSRIs in anxiety is comparable.
- SNRIs are effective in the treatment of chronic pain, whereas SSRIs are generally not useful.
- Venlafaxine seems to be the least well-tolerated SNRI, combining a high level of serotonergic adverse effects (nausea, sexual dysfunction, withdrawal problems) with dose-dependent hypertension. In contrast, duloxetine and milnacipran appear better tolerated and essentially devoid of cardiovascular toxicity.

ABSTRACT

The class of serotonin and norepinephrine reuptake inhibitors (SNRIs) now comprises three medications: venlafaxine, milnacipran, and duloxetine. These drugs block the reuptake of both serotonin (5-HT) and norepineph-

rine with differing selectivity. Whereas milnacipran blocks 5-HT and norepinephrine reuptake with equal affinity, duloxetine has a 10-fold selectivity for 5-HT and venlafaxine a 30-fold selectivity for 5-HT. All three SNRIs are efficacious in treating a variety of anxiety disorders. There is no evidence for major differences between SNRIs and SSRIs in their efficacy in treating anxiety disorders. In contrast to SSRIs, which are generally ineffective in treating chronic pain, all three SNRIs seem to be helpful in relieving chronic pain associated with and independent of depression. Tolerability of an SNRI at therapeutic doses varies within the class. Although no direct comparative data are available, venlafaxine seems to be the least well-tolerated, combining serotonergic adverse effects (nausea, sexual dysfunction, withdrawal problems) with a dose-dependent cardiovascular phenomenon, principally hypertension. Duloxetine and milnacipran appear better tolerated and essentially devoid of cardiovascular toxicity.

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INTRODUCTION

Virtually without exception all effective antidepressants increase the synaptic concentrations of serotonin (5-HT) and/or norepinephrine (NE), usually by blocking the reuptake of one or both of the neurotransmitters. This common property of antidepressants was discovered initially with tricyclic antidepressants (TCAs), which, depending on the particular compound, block NE and/or 5-HT transporters.^{1,2} However, the various additional interactions of TCAs at a variety of neurotransmitter

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receptors result in poor tolerability and toxicity in overdose.^{1,3} Other than patients who do not respond to other antidepressants, the use of TCAs is now limited to patients who cannot afford (or their health-care providers will not reimburse) safer and better tolerated but more expensive drugs.

Compounds that selectively block the reuptake of 5-HT, selective serotonin reuptake inhibitors (SSRIs), are effective and well-tolerated antidepressants.^{1,2} Similarly, a selective inhibitor of the reuptake of NE, such as reboxetine, also has antidepressant activity.⁴ Thus, it appears that a selective action on one or the other of the monoamines is sufficient for antidepressant activity.⁵

The limited efficacy of all antidepressants with response rates of 60% to 70% and remission rates usually <50%, however, has spurred continued research for improved antidepressants. The idea that "two actions are better than one" has led to the development of compounds that prevent the reuptake of both 5-HT and NE without the nonspecific, side effect-inducing interactions of TCAs. These are serotonin and norepinephrine reuptake inhibitors (SNRIs).

The recent commercialization of duloxetine, the third in the class after venlafaxine and milnacipran, (Figure 1), makes it possible to speak of a true class of compounds and to review their common properties and to attempt to separate hype from clinical reality in terms of comparison with other classes of antidepressant.

A fourth SNRI, sibutramine, has been exclusively developed for the treatment of obesity.⁶

PHARMACOLOGY: SIMILARITIES AND DIFFERENCES BETWEEN VENLAFAXINE, MILNACIPRAN, AND DULOXETINE

In Vitro Studies

By definition, the three SNRIs inhibit the 5-HT and NE transporters. There is, however, considerable difference in their affinities and their selectivity (Figure 2).

Venlafaxine has a high affinity for the 5-HT



FIGURE 1. Chemical structures of venlafaxine, milnacipran, and duloxetine

C=carbon; H=hydrogen; N=nitrogen; O=oxygen; S=sulfur.

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transporter but not the NE transporter and at low doses probably acts as an SSRI. Duloxetine has a more balanced affinity but is still more selective for the 5-HT transporter. Milnacipran is the most balanced and may even be slightly more noradrenergic than serotonergic. Its high affinity for both the transporters suggests that its therapeutic effects are likely to be similar to TCAs but without the poorer side-effect profile. Similarly duloxetine probably acts on both neurotransmitters at all doses, whereas the dual-action mechanism of venlafaxine is dose-dependent with significant NE reuptake inhibition only occurring at higher doses.

Venlafaxine and duloxetine, but not milnacipran, have a low affinity for the dopamine transporter, which may be clinically relevant at higher doses, especially for venlafaxine.⁷

Microdialysis Studies

The logical and expected consequence of the inhibition of monoamine reuptake is an increase of synaptic concentrations of the monoamines. The extracellular levels of the monoamines in brain regions can be measured using the microdialysis technique in conscious, freely moving animals.⁹ This method, which can measure changes in a variety of neurotransmitters following systemic administration of drugs, can be used to demonstrate the specificity

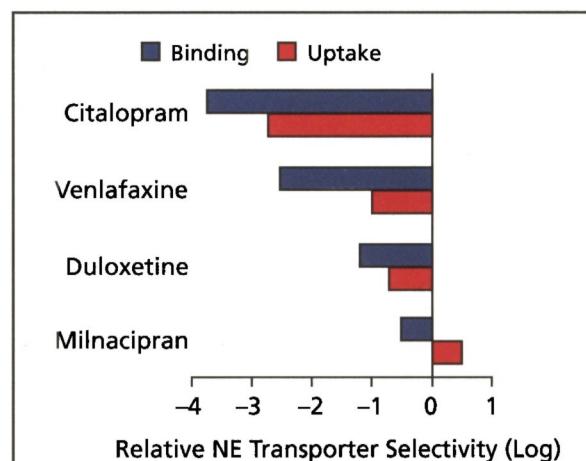


FIGURE 2. Selectivity for 5-HT versus NE transporter binding and uptake inhibition*

* Positive numbers: more selective uptake inhibition and binding for NE transporter than 5-HT transporter. Negative numbers: more selective for 5-HT transporter than NE transporter.

Adapted with permission from the *Journal of Clinical Psychiatry*. Owens MJ. Selectivity of antidepressants: from the monoamine hypothesis of depression to the SSRI revolution and beyond. *J Clin Psychiatry*. 2004;65(suppl4):5-10.

NE=norepinephrine; 5-HT=serotonin.

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of the administered compounds. For example, the SNRIs reboxetine and atomoxetine have been shown to increase extracellular levels of NE but not 5-HT in various brain regions.¹⁰ In contrast, the SSRIs citalopram, paroxetine, and sertraline selectively enhance extracellular concentrations of 5-HT.¹¹

The effects of the three SNRIs on the extracellular levels of 5-HT and NE have been extensively studied in several brain regions and in different species.^{12,13} In freely moving rats, a subcutaneous (SC) administration of venlafaxine 10 mg/kg significantly enhanced the levels of NE but not 5-HT in the neocortex.¹⁴ Similarly, venlafaxine 10, 30, and 50 mg/kg SC significantly enhanced the levels of NE but not 5-HT in the frontal cortex.¹⁵ Koch and colleagues,¹⁶ however, found dose-dependent increases of both 5-HT and NE concentrations in microdialysates from the prefrontal cortex of the conscious rats after administration of venlafaxine 5–40 mg/kg intraperitoneal injection (IP). Similar increases of 5-HT and NE were also obtained in the rat frontal cortex^{18,19} and hippocampus.²⁰ In the hypothalamus of freely moving guinea pigs, extracellular 5-HT was significantly and dose-dependently increased following administration of venlafaxine >40 mg/kg IP.²¹ NE levels, however, were only enhanced with 160 mg/kg dose. Greater increases of 5-HT output compared with that of NE were also obtained in the frontal cortex of freely moving mice after administration of venlafaxine 8 mg/kg IP.²²

The oral administration of milnacipran 10 and 30 mg/kg produced dose-related similar increases in both extracellular 5-HT and NE concentrations measured in the medial prefrontal cortex of rats.²³ Equivalent findings were previously obtained in guinea pig hypothalamus, using milnacipran 10 mg/kg and 40 mg/kg IP.²⁴ In contrast, in another study,¹⁶ the administration of milnacipran 5 mg/kg IP resulted only in a minimal increase in 5-HT or NE extracellular levels in prefrontal cortex of freely moving rats. Even at 40 mg/kg IP, Koch and colleagues¹⁶ found only small increases in NE levels and even smaller increases in 5-HT.

The oral administration of duloxetine 3.125–12.5 mg/kg produced a dose-dependent increase in the output of extracellular levels of both 5-HT and NE in

TABLE 1. IN VITRO AND IN VIVO INHIBITION OF MONOAMINE TRANSPORTERS BY SNRIS

	5-HT	NE	D	Selectivity 5-HT/NE/D
In vitro inhibition of binding to human monoamine transporter Ki (nM)				
Venlafaxine	82*	2,483*	7,647*	1/30/93
	7.8†	1,920†	6050†	1/246/776
Milnacipran	123 *	200*	>10,000*	1/1.6/-
	8.4†	22†	>100,000†	1/2.6/-
Duloxetine	0.8*	7.5*	240*	1/9.4 /300
	0.07†	1.2†	230†	1/17.1/3,286
In vitro inhibition of human monoamine uptake Ki (nM)				
Venlafaxine	145†	1,420†	3,070†	1/9.8/21
Milnacipran	151†	68†	>100,000†	1/0.5/662
Duloxetine	3.7†	20†	439†	1 /5.4/119
In vivo inhibition of monoamine reuptake in rat brain ED50 (mg/kg IP)				
Venlafaxine	5.9*	>100*	—	1/>17
Milnacipran	24.6*	43.5*	—	1/1.8
Duloxetine	2.3*	14.9*	—	1/6.5

* Compiled from data by Koch et al¹⁶

† Compiled from data by Vaishnavi et al¹⁷

SNRIs=serotonin and norepinephrine reuptake inhibitors; 5-HT=serotonin; NE=norepinephrine; D=dopamine; —=not studied/not calculable; Ki=kinetic inhibition; nM=nanometer; ED50=effective dose 50; IP=intraperitoneal injection.

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the frontal cortex of freely moving rats.²⁵ Duloxetine 5 mg/kg SC elicited increases in 5-HT and NE in frontal cortex.²⁶ Duloxetine administration at 4 mg/kg, 7 mg/kg, and 15 mg/kg IP in freely moving rats dose-dependently enhanced 5-HT (significant only at 15 mg/kg) and NE (significant at the two higher doses) in the hypothalamus.²⁷ Duloxetine 5 mg/kg IP increased the output of 5-HT and NE about equally, and to a greater extent, at 15 mg/kg IP, the effect being larger for NE at 15 mg/kg.¹⁶

The considerable variability found between studies may result from the use of different brain regions, routes of administration, species, and microdialysis techniques. For example, the increase in the extracellular levels of 5-HT following the administration of venlafaxine was higher in the hippocampus than in the frontal cortex of freely moving rats.²⁸ For milnacipran, the comparison of two different studies^{7,24} suggests that increases are smaller in the cortex than in the hypothalamus. Bel and Artigas,²⁹ who studied the effect of milnacipran on 5-HT in both regions, found that in the rat frontal cortex 5-HT output was only increased from 60 mg/kg SC (1 mg/kg SC, 10 mg/kg SC, and 30 mg/kg SC produced no significant effect). In contrast, in the hypothalamus a clear-cut enhancement was produced by milnacipran 10 mg/kg SC. Mochizuki and colleagues,²³ however, found effects on both 5-HT and NE in the rat medial frontal cortex following oral administration of milnacipran that were similar to those reported previously²⁴ in guinea pig hypothalamus. With regard to duloxetine, the effect on 5-HT output was greater in the diencephalon than in the frontal cortex of freely moving rats.³⁰

In summary, systemic administration of all three SNRIs results in increases in extracellular levels of both 5-HT and NE in various brain regions. In certain studies^{6,11,12,15,19-22} there is evidence for a selectivity between the neurotransmitters but currently the contradictions between studies make it difficult to draw any firm conclusions.

Clinical Pharmacology

All three SNRIs have been shown to inhibit the reuptake of 5-HT into platelets in humans.³¹⁻³³ Indirect evidence from in vitro binding, in vivo uptake and microdialysis studies in animals suggests that venlafaxine selectively inhibits 5-HT uptake at low doses, whereas at higher doses, it inhibits both 5-HT and NE uptake. Studies with duloxetine^{32,34} suggest a similar profile but with noradrenergic effects occurring at doses closer to those giving serotonergic effects. Finally, milnacipran would be expected to produce

noradrenergic and serotonergic effects at similar doses.

Studies in healthy human volunteers³¹ have shown that the pressor response to tyramine, a marker of NE reuptake, is reduced following a high (375 mg/day) but not a low (75 mg/day) dose of venlafaxine (Table 2).^{31,32,34,36} Similar studies with duloxetine^{32,34} showed no effect at doses from 20–120 mg/day although certain other effects, such as increased blood pressure, suggest some effect on NE reuptake at higher doses (Table 2). To date, there are no studies with milnacipran of the inhibition of NE reuptake in humans.

Pharmacokinetics

All three SNRIs are rapidly absorbed after oral administration.³⁷⁻³⁹ Compared with many of the SSRIs, the SNRIs have relatively short half-lives, ranging from 4 hours for venlafaxine (10 hours for its principal active metabolite, O-desmethylvenlafaxine), 8 hours for milnacipran, and 12 hours for duloxetine. Although initially recommended for twice-daily administration, usage with all three is tending toward once-daily administration, through an extended-release (ER) formulation for venlafaxine or a switch to once-daily administration once steady-state has been achieved (duloxetine and milnacipran). Venlafaxine and duloxetine are metabolized by the cytochrome P450 isoenzyme 2D6 and their metabolism is therefore modified by medication that inhibits this enzyme. In addition duloxetine and, to a lesser extent, venlafaxine are both inhibitors of this enzyme so they modify the elimination of compounds metabolized by this enzyme. Although clinically significant, the degree of inhibition with venlafaxine is, however, less than with certain SSRIs, such as paroxetine, fluoxetine, fluvoxamine, and sertraline.⁴⁰ The effect of duloxetine is approximately comparable with that of sertraline. The only SNRI that is free from metabolic drug-drug interactions is milnacipran, which is only metabolized to a very limited extent and has been shown not to interfere with the cytochrome P450 enzymes in any way.^{37,41}

CLINICAL STUDIES OF SNRIS IN COMPARISON WITH SSRIs

Depression

There have been no published studies comparing the SNRIs between themselves, although a recent poster presentation⁴² suggested that the efficacy and tolerability of venlafaxine and duloxetine were globally comparable. However, comparison of studies in which each SNRI has been compared with one or more SSRIs (Table 3) suggests⁴³⁻⁴⁷ that the level

of efficacy of the three SNRIs is globally similar. Further data and especially direct comparative data between the SNRIs are required before any firm conclusions can be made as to their relative efficacy.

Since the introduction of SNRIs the question of their real or imagined superior efficacy to SSRIs has been a subject of controversy. A large meta-analysis⁴⁸ concluded that TCAs showed superior efficacy compared with SSRIs. This superiority, however, was limited to more severely depressed patients. In addition, only "dual action" TCAs, which inhibited the reuptake of both NE and 5-HT, were superior to SSRIs.⁴⁹⁻⁵¹ Additional evidence^{5,52} suggests that combining a specific norepinephrine reuptake inhibitor, such as desipramine, with an SSRI, such as fluoxetine, can result in a greater efficacy. Thus there was a clear expectation that the SNRI would produce efficacy superior to SSRIs.

Venlafaxine has been the most studied of the SNRIs. There exists a large number of studies comparing venlafaxine with various SSRIs and a number of meta-analyses have shown a superior efficacy of the SNRI compared with SSRIs. A meta-analysis of 19 studies⁵³ showed superior efficacy of venlafaxine over fluoxetine and possibly other SSRIs. The efficacy of venlafaxine is clearly dose-dependent, in contrast to efficacy with the SSRIs.^{54,55} Venlafaxine at low doses inhibits almost exclusively the reuptake of 5-HT.³¹ As the dose is increased the reuptake of NE is progressively inhibited. It is generally accepted that clinically meaningful NE reuptake inhibition is only achieved beyond 150 mg/day. As would be expected, the superior efficacy of venlafaxine over the SSRIs is only seen when doses >150 mg/day are used.^{56,57}

A pooled analysis of original data from eight randomized, double-blind studies, including more than

TABLE 2. NORADRENERGIC EFFECTS IN HUMANS WITH VENLAFAXINE AND DULOXETINE*^{31,32,34-36}

Noradrenergic Activity (in vivo)	Venlafaxine XR			Duloxetine			
	75 mg	150 mg	≥225 mg	20 mg	60 mg	80 mg	≥120 mg
Tyramine pressor response	-	NT	+	-	-	-	+/-
Acute BP changes†	+	+	NT	-	+	+	-
Standing heart rate	-	-	NT	-	-	+/-	+
Supine heart rate	-	-	NT	-	-	-	(≥160 mg only) +
Plasma NE	NT	NT	NT	-	-	+	+

* Dose schedules were not consistent; drugs were administered either QD or BID.

† Acute BP changes include changes in systolic, diastolic, standing, or supine.

XR=extended release; -absent; NT=not tested; +present; +/-=varying results; BP=blood pressure; NE=norepinephrine.

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TABLE 3. ANTIDEPRESSANT RESPONSE AND REMISSION RATES OF SNRIs IN COMPARATIVE TRIALS WITH SSRIs

	Milnacipran*	SSRI	Venlafaxine†	SSRI	Duloxetine‡	SSRI
Response§	64%	50%	64% [¶]	57%	51%	40%
Remission#	39%	28%	45% ^{**}	35%	50%	37%

* Taken from a meta-analysis comparing milnacipran 100 mg/day (n=1,871) and SSRIs.^{43,44}

† Taken from a pooled analysis of venlafaxine (IR and XR) used at variable doses from 75–225 mg/day (n=851) and SSRIs (n=748).^{45,46}

‡ Taken from a comparative study of duloxetine 40 mg/day (data not shown) and 80 mg/day (n=91) and paroxetine 20 mg/day (n=87).⁴⁷

§ Response rate is the percentage of patients having a reduction of ≥50% in their HAM-D score between baseline and endpoint.

|| P<.05 compared with SSRIs.

¶ P<.01 compared with SSRIs.

Remission rate is the percentage of patients having a HAM-D score ≤8 at endpoint.

** P<.001 compared with SSRIs.

SNRIs=serotonin and norepinephrine reuptake inhibitors; SSRIs=selective serotonin reuptake inhibitors; IR=immediate release; XR=extended release; HAM-D=Hamilton Depression Rating Scale.

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2,000 patients with major depressive disorder,⁴⁵ compared the remission rates in patients treated with venlafaxine with those of patients treated with SSRIs. It found that 45% of venlafaxine-treated patients remitted compared with 35% of those given an SSRI and 25% of those given placebo. These results did not depend on inclusion of any one particular study nor the definition of remission used. A similar analysis of the same studies⁴⁶ found significantly greater response rates for venlafaxine compared with SSRI on all scales used. A related analysis⁵⁸ reported that this advantage was apparent for both men and women across all ages.

The most recent pooled analysis⁵⁹ (Figure 3) included data from 32 Wyeth-sponsored double-blind studies ($N=3,300$) that compared venlafaxine (including venlafaxine extended release [XR]) with an SSRI ($n=3,236$)—fluoxetine [$n=1,673$], paroxetine [$n=680$], and sertraline [$n=652$], citalopram [$n=197$], fluvoxamine [$n=34$]—that have been carried out to date. Nine studies had a placebo control group ($N=927$). The doses used in the studies were venlafaxine 75–375 mg/day, venlafaxine XR 75–300 mg/day, fluoxetine 20–80 mg/day, paroxetine 20–40 mg/day, sertraline 50–200 mg/day, citalopram 20–60 mg/day, and fluvoxamine 100–200 mg/day. The remission rate (Figure 3) for the SNRI was significantly ($P<.001$) greater than that produced by the SSRIs, which in turn was significantly greater ($P<.001$) than that produced by placebo.

Not all data, however, support superior remission rates with SNRIs compared with SSRIs. Indeed ~20% of the Wyeth-sponsored SSRI comparative studies in the meta-analysis discussed above,⁵⁹ actually favored, at least numerically, the SSRI. An 8-week study⁶⁰ compared remission rates of venlafaxine XR 75–225 mg/day ($n=79$) and the SSRI sertraline 50–150 mg/day ($n=79$). There was no significant difference between the remission rates, which were high for both agents (54% and 60%, respectively) in this relatively small study that did not include a placebo arm. It is interesting to note that in addition to its activity in inhibiting the reuptake of 5-HT, sertraline is also an effective inhibitor of dopamine reuptake.⁶¹

Similarly, an 8-week study comparing 100 patients on fixed-dose venlafaxine XR 225 mg/day after a very rapid titration with escitalopram 20 mg/day ($n=98$)⁶² failed to show any significant difference in remission rates (31.6% and 36.1% for venlafaxine and escitalopram, respectively). The interpretation of this study is also limited by the lack of a placebo arm. Another similar study,⁶³ also with-

out a placebo arm, comparing a more limited dose range of venlafaxine XR 75–150 mg/day ($n=148$) with escitalopram 10–20 mg/day ($n=145$), also failed to show any significant difference in efficacy between the two antidepressants. A post hoc analysis suggested, however, that escitalopram-treated patients achieved sustained remission significantly faster than venlafaxine-treated patients. However, since not all of the outcome measures were reported this study is difficult to interpret.

There are less studies available with milnacipran but a meta-analysis of studies comparing milnacipran with the SSRIs fluvoxamine and fluoxetine in hospitalized moderate to severely depressed patients^{43,44} reported significantly more responders (64%) with milnacipran than with the SSRI (50% $P<.01$) and a significantly higher remission rate (38.7% versus 27.6% $P<.04$). This meta-analysis was not, however, inclusive of all comparative SSRI studies, including only those carried out with milnacipran 100 mg/day. Another study,⁶⁴ published subsequent to this meta-analysis, which compared milnacipran and paroxetine in less severely depressed outpatients reported similar remission rates for the two antidepressants.

Table 4 summarizes two studies,^{52,65} each comparing milnacipran with an SSRI, one in moderate to severely depressed inpatients and the other in mild to moderately depressed outpatients. Examination of the data suggests that when a reduction of the Montgomery Åsberg Depression Rating Scale score

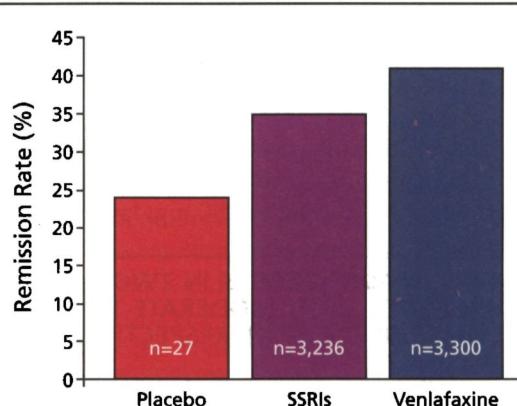


FIGURE 3. Cumulative remission rates with SNRIs, SSRIs, and placebo*⁵⁹

* Pooled data were gathered from 32 double-blind, randomized, controlled trials. All studies had similar methodologies and statistical evaluations. The trials took place worldwide. The included SSRIs were: fluoxetine, paroxetine, sertraline, citalopram, and fluvoxamine. All comparisons were statistically significant, $P<.001$. Based on data from Nemerooff et al.

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of ~17 was required to bring about significant recovery (as in the outpatient study) the SSRI was as efficacious as the SNRI. In the more severely depressed patients, where a decrease of ~24 points was required to attain the same level of recovery, the effect of the SSRI was still limited to ~17 points. This analysis is only indicative because the severity of depression was probably not the only variable that differed between the studies and, indeed, the SSRIs used were not the same. Nevertheless, the results are compatible with other data⁶⁶ suggesting that SSRI have a limited capacity for improving depressive symptoms that may not be noticeable in less severely depressed patients. However, when the depression is more severe, the difference becomes more evident.

An interesting observation was made in the study comparing milnacipran with paroxetine.⁶⁴ Although, overall, the efficacy of the two antidepressants was similar, there was a significantly superior effect of milnacipran compared with paroxetine in the subgroup of patients scoring maximally on item 8 of the Hamilton Depression Rating Scale (retardation-slowness of thought and speech; impaired ability to concentrate; decreased motor activity). This is indicative of a subpopulation of depressed patients who may particularly benefit from the prescription of an SNRI.

Two studies comparing duloxetine with paroxetine and placebo have been published.^{47,67} One study⁴⁷ failed to find any significant superiority of paroxetine over placebo. In this study, treatment with duloxetine 80 mg/day, but not 40 mg/day, was associated with a significantly greater "estimated probability of remission" than paroxetine or placebo. Response rates were 31% in the placebo group; 40% for paroxetine 20 mg/day; 44% for duloxetine 40 mg/day; and 51% for duloxetine 80 mg/day. Only the duloxetine 80 mg/day group was

significantly different from placebo. In the second study,⁶⁷ duloxetine 80 mg/day and 120 mg/day and paroxetine 20 mg/day were all significantly superior to placebo. The two doses of duloxetine were not, however, significantly different from paroxetine.

Although these are the only studies comparing duloxetine with SSRI that have been published to date, other studies have been carried out. A pooled analysis of six placebo-controlled studies,⁶⁸ including two against fluoxetine 20 mg/day and one against paroxetine 20 mg/day, have been presented as a poster. Although treatment with a SSRI in 423 subjects resulted in a numerically higher remission rate than placebo (n=507), the difference was not significant. In contrast, significantly more duloxetine 80 mg/day and 120 mg/day (n=697) achieved remission than patients treated with placebo. The difference between remission rates with duloxetine and the SSRI was not, however, significant. Since these studies were carried out with high doses of duloxetine 80 mg/day and 120 mg/day, it is difficult to estimate the level of efficacy that is to be expected of duloxetine 60 mg/day, which is the maximum dose recommended by the Food and Drug Administration for duloxetine in the treatment of major depression (United States product information sheet).⁶⁹

Although some individual studies show comparable remission rates for SSRI and SNRI (sertraline versus venlafaxine⁶⁰; escitalopram versus venlafaxine⁶²; and paroxetine versus milnacipran⁶⁴) and possibly even superior efficacy of SSRI (escitalopram versus venlafaxine⁶³), the majority of data including a recent large pooled analysis⁵⁹ show higher remission rates with dual-action agents. Having said this, this conclusion is based largely on studies using venlafaxine. There are still insufficient studies with the newer SNRIs, milnacipran and duloxetine, to draw definitive conclu-

TABLE 4. MADRS SCORES IN TWO SIMILAR STUDIES COMPARING MILNACIPRAN AND AN SSRI IN INPATIENTS WITH MODERATE-TO-SEVERE DEPRESSION AND OUTPATIENTS WITH MILD-TO-MODERATE DEPRESSION, RESPECTIVELY

<u>Mean MADRS Score</u>	Moderate-to-Severe Depression Inpatients ⁶⁵		Mild-to-Moderate Depression Outpatients ⁵²	
	<u>Milnacipran</u>	<u>Fluvoxamine</u>	<u>Milnacipran</u>	<u>Paroxetine</u>
Baseline	37.1	35.5	28.9	29.6
Endpoint (42 days)	12.9	18.1	13.6	12.8
Difference (baseline–endpoint)	24.2*	17.4	15.3	16.8

* P<.01 compared with the difference with fluvoxamine.

MADRS=Montgomery-Åsberg Depression Rating Scale; SSRI=selective serotonin reuptake inhibitor.

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sions for the class. Similarly many of the comparisons are with fluoxetine and to a lesser extent paroxetine. Data with sertraline and escitalopram are still rare and it is still too early to generalize to all SSRIs.

Anxiety Disorders

All anxiety disorders combined have a 1-year prevalence rate of 13% to 17%.^{70,71} In addition nearly 70% of depressed patients also suffer from generalized anxiety disorder (GAD) or some other anxiety disorder. According to certain theories, the noradrenergic effect of the SNRIs might be expected to exacerbate anxiety symptoms.⁷² Results with venlafaxine, and, to a lesser extent, with duloxetine and milnacipran, suggest, however, that not only is this not true but that the SNRIs are effective at relieving symptoms in a wide range of anxiety disorders.

The probable role of abnormal serotonergic neurotransmission in anxiety is widely accepted^{73,74} and SSRIs have become widely used in the treatment of a variety of chronic anxiety disorders.^{73,75-77} While the role of NE is less clear, substantial evidence supports the idea that a disturbed noradrenergic neurotransmission contributes to the symptoms of anxiety.^{73,78,79} Thus, it appears likely that modulation of both 5-HT and NE systems as produced by SNRIs should be helpful in the treatment of anxiety disorders and could conceivably produce a greater effect than compounds selective for a single neurotransmitter.⁷¹

Most of the randomized clinical trials have evaluated venlafaxine, which has been studied in the treatment of GAD, social anxiety disorder, panic disorder, posttraumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD).⁷¹

The efficacy of venlafaxine ER in the short-term treatment of GAD is supported by three 8-week placebo-controlled trials.⁸⁰⁻⁸² Two long-term studies^{83,84} have confirmed that this activity is maintained for at least 6 months. Evidence for a dose-dependent response is somewhat inconsistent but globally it appears that venlafaxine ER 150 mg/day, a true SNRI dose, is probably required for activity in GAD.

Four placebo-controlled trials⁸⁵⁻⁸⁸ support the activity of venlafaxine ER in social anxiety disorder. Two of the studies included paroxetine as a comparator. In one of the studies,⁸⁸ venlafaxine ER was significantly superior to paroxetine on some parameters.⁸⁵

In panic disorder, venlafaxine has been shown to be superior to placebo in two out of three trials.^{89,90} In the third trial,⁹¹ venlafaxine was superior to placebo on a series of secondary parameters although significance was not achieved on the primary outcome measure (percentage of patients free from

full-symptom panic attacks). In one study,⁹⁰ where paroxetine was used as a comparator, no difference was found between venlafaxine and the paroxetine.

Venlafaxine 37.5–300 mg/day has been examined in PTSD in a single placebo-controlled trial with sertraline 25–200 mg/day.⁹² From week 2 through to the end of the 12-week trial, venlafaxine was significantly superior to placebo. In contrast, sertraline was not superior to placebo. Remission rates at the end of the study were 30% (venlafaxine), 24% (sertraline), and 20% (placebo).

No placebo controlled trials are available for OCD but in a 12-week double-blind comparison of venlafaxine ≤300 mg/day and paroxetine ≤60 mg/day both compounds were found to be equally efficacious.⁹³

As indicated earlier, nearly 70% of depressed patients also suffer from GAD or another anxiety disorder. Venlafaxine has been extensively tested in this category of patient in comparison with fluoxetine.⁷¹ In a meta-analysis of these studies in patients with depression and anxiety,⁹⁴ venlafaxine was found to have superior efficacy to fluoxetine against both depressive and anxiety symptoms. Response rates were significantly superior from 3 weeks and remission rates from 2 weeks. Specifically venlafaxine was particularly effective in treating psychic anxiety symptoms especially in patients with moderate to severe anxiety levels.

Milnacipran has not yet been studied in anxiety disorders in randomized trials but data from an open trial⁹⁵ suggest that it may also be effective in the treatment of anxiety.

Anxiety has been analyzed as a secondary outcome parameter in various placebo and/or comparator controlled trials with duloxetine. A pooled analysis of the efficacy of duloxetine in treating anxiety symptoms⁹⁶ concluded that the SNRI was associated with significant relief of anxiety symptoms compared with placebo and was significantly better than the comparator SSRIs paroxetine and fluoxetine.

Thus, from the currently available data, it appears that the SNRIs are effective in a wide range of anxiety disorders with efficacy equal to or greater than that of the SSRIs.

Chronic Pain

It has been repeatedly suggested that pain and depression may share a common psychopharmacology,⁹⁷⁻¹⁰⁰ implying that compounds inhibiting the reuptake of 5-HT and/or NE are likely to be effective in the relief of chronic pain¹⁰¹ and other physical symptoms.¹⁰² There are indications that the role of NE is more important than that of 5-HT in the relief

of pain.¹⁰³ Indeed, various neuropathic pain syndromes, such as diabetic neuropathy and post-herpetic neuralgia,¹⁰⁴ respond to dual-action TCAs but not to SSRIs. A meta-analysis of studies of various antidepressants in the treatment of chronic lower-back pain found that TCAs and tetracyclic antidepressants, which inhibit NE reuptake, were moderately effective in reducing pain, whereas SSRIs did not appear to be helpful.¹⁰⁵

Open trials have suggested the efficacy of venlafaxine in a number of chronic pain syndromes,⁹⁹ including fibromyalgia.¹⁰⁶ The efficacy suggested by these open studies has been confirmed in a double-blind, placebo-controlled trial in diabetic neuropathy,¹⁰⁷ where venlafaxine ER, at doses (150–225 mg/day) which inhibit the reuptake of both NE and 5-HT, produced significantly greater pain relief than placebo. A double-blind, placebo-controlled, three-way crossover study in painful neuropathy¹⁰⁸ compared the effectiveness of venlafaxine 225 mg/day and imipramine 150 mg/day with placebo. Both antidepressants produced relief from pain which was significantly greater than that achieved with placebo. Results between the two antidepressants were not significantly different. Finally, a small placebo-controlled crossover study of 13 patients suffering from neuropathic pain¹⁰⁹ following the treatment for breast cancer showed that venlafaxine significantly reduced maximal pain intensity.

The capacity for milnacipran to relieve chronic pain has also been demonstrated in open trials⁹⁹ in a range of syndromes, including glossodynia, orthopedic pain, and fibromyalgia. A placebo-controlled study of milnacipran in fibromyalgia¹¹⁰ showed that 37% of the patients treated twice daily with milnacipran 200 mg/day reported a reduction in pain intensity of 50% or more compared with only 14% of placebo-treated patients ($P<.05$).

In a double-blind, placebo-controlled study¹¹¹ in patients with major depression, duloxetine 60 mg/day produced a statistically significant reduction in pain severity compared with placebo as evaluated by a visual analogue scale and the somatic symptom inventory. This effect was confirmed in another study comparing duloxetine 60 mg/day with placebo in depressed patients with associated painful symptoms.¹¹² In this study, the SNRI was shown to be an effective treatment for the painful physical symptoms associated with depression even though it was not significantly superior to placebo in the treatment of the depressive symptoms as judged by the classical rating scales.

Duloxetine 120 mg/day improved fibromyalgia symptoms and pain severity regardless of the extent of the accompanying depressive disorder. In female patients, duloxetine (n=92) produced significantly

greater improvement on most efficacy measures compared with placebo treatment (n=92). In male patients (n=12 in each group), however, the difference was not significant.¹¹³ Thus, considerable evidence suggests that SNRIs are effective in relieving chronic pain in a variety of disorders both associated with, and independent of, depression. There is less evidence to show that they are superior to SSRIs in this activity.

Early studies¹⁰³ suggested that an action on the noradrenergic system alone or in combination with a serotonergic action is required for pain relief and that the SSRIs are, at best, only weakly active. TCAs and venlafaxine have been shown to be effective in several chronic neuropathic pain syndromes, such as postherpetic neuralgia, diabetic neuropathy, and fibromyalgia; whereas SSRIs, such as fluoxetine or citalopram, have not shown activity.^{104,114,115} In an extensive review of the pre-clinical and clinical data, Fishbain and colleagues¹⁰¹ determined that, overall, dual-acting antidepressants were more active than norepinephrine reuptake inhibitors, which were more active than SSRIs.

There have, however, been some reports suggesting that some SSRIs may be effective to some extent in relieving pain. For example, a placebo-controlled trial¹¹⁶ showed significant effectiveness of fluoxetine for reducing pain and other symptoms in a group of women suffering from fibromyalgia. A meta-analysis¹¹⁷ of 94 placebo-controlled studies in which a variety of physical symptoms and pain disorders, including headache, gastrointestinal pain, tinnitus, fibromyalgia, and chronic fatigue, had been treated with a range of antidepressants, including TCAs and SSRIs, concluded that all of the antidepressants produced a similar degree of relief. A subsequent meta-analysis of 13 placebo-controlled studies in fibromyalgia¹¹⁸ by the same authors came to a similar conclusion. In a recent, small double-blind study,¹¹⁹ which compared the pain relieving effect of the SSRI citalopram and the norepinephrine reuptake inhibitor reboxetine in 35 patients suffering from somatoform pain disorder, only citalopram was found to produce a significant effect. Due to the small size of this study, a replication is essential before any conclusions can be drawn.

In 2003, a meta-analysis of seven studies of antidepressants in the treatment of chronic lower-back pain¹⁰⁵ confirmed that TCAs and tetracyclic antidepressants, which inhibit NE reuptake, produced moderate symptom relief, whereas SSRIs were inactive. A pooled analysis of 31 double-blind studies comparing venlafaxine with SSRIs¹⁰² found that the SNRI was significantly more effective than SSRIs in treating somatic symptoms associated with depression. In particular, the proportion of patients with full remission

of their somatic symptoms was significantly greater with venlafaxine than with an SSRI.

To date, it is fair to say that dual-acting antidepressants (both TCAs and SNRIs) clearly produce significant relief of physical symptoms, such as pain in depression and in a variety of chronic pain syndromes. The evidence that SSRIs may produce similar effects is less consistent. Where comparative studies are available, they invariably indicate a superiority of the dual-acting agents. With the development of milnacipran and duloxetine focusing on their ability to bring relief in chronic pain, more extensive comparative data should be forthcoming to make a more evidence-based judgment on the superiority of the SNRI in these indications.

TOLERABILITY OF SEROTONIN REUPTAKE INHIBITORS IN COMPARISON WITH SSRIs

General Tolerability

All three SNRIs are generally well-tolerated, most adverse events occurring early in treatment with a mild to moderate severity and with a tendency to decrease or disappear with continued treatment.^{44,120,121} The frequency of adverse events in clinical trials depends on a large number of factors so that comparisons between studies or meta-analyses can be hazardous. Nevertheless, in the absence of direct comparative studies, this type of comparison can give an approximate idea of the relative tolerability of different compounds, especially if there is a common comparator group, in this case the SSRIs. Table 5 shows the occurrence of adverse events at clinically effective doses in comparison with SSRIs taken from meta-analyses or pooled analyses.^{43,46,47} For duloxetine, the only study currently published, comparing it to paroxetine, was used.

The most frequent adverse event for all three SNRIs and for the SSRIs is nausea. Globally, the frequency of nausea with the SNRIs is approximately similar to the SSRIs, possibly slightly more frequent with venlafaxine and duloxetine and less frequent with milnacipran (Table 5). In general, the three SNRIs show a similar pattern of adverse effects. The frequency of these effects would appear to be somewhat less with milnacipran but this impression needs to be confirmed by direct head-to-head comparisons of equally effective doses. As would be expected, adverse effects that are probably related to a noradrenergic stimulation, such as dry mouth, sweating, and constipation, are found systematically more frequently with the SNRIs than the SSRIs, although the differences are not as large as might be expected.

Sexual Dysfunction

When SSRIs were initially introduced, they were considered almost side-effect free. However, their widespread use has shown that this class of antidepressant is not without its drawbacks. It has become apparent that sexual dysfunction is a frequent problem for patients taking SSRIs, with some postmarketing clinical trials reporting rates as high as 75%.¹²² Sexual dysfunction caused by SSRIs, principally anorgasmia in women and decreased libido in both

TABLE 5. PERCENTAGE OCCURRENCE OF ADVERSE EVENTS OF THE DIFFERENT SNRIs COMPARED WITH SSRIs

Adverse Event	<u>Lopez-Ibor et al^{*43}</u>		<u>Stahl et al^{†46}</u>		<u>Goldstein et al^{‡47}</u>	
	<u>Milnacipran (%)</u>	<u>SSRI (%)</u>	<u>Venlafaxine (%)</u>	<u>SSRI (%)</u>	<u>Duloxetine (%)</u>	<u>SSRI (%)</u>
Nausea	11	20	24	18	25	16
Vertigo/dizziness	5	4	13	7	17	10
Dry mouth	8	4	12	8	15	8
Insomnia	6	5	11	10	20	8
Somnolence	2	3	5	7	11	8
Sweating	4	3	10	8	12	7
Constipation	7	5	9	4	9	14

* Taken from a meta-analysis comparing milnacipran 100 mg/day (n=1,871) and SSRIs.

† Taken from a pooled analysis of venlafaxine (IR and XR) used at variable doses from 75–225 mg/day (n=895) and SSRIs.

‡ Taken from a comparative study of 80 mg/day (n=91) and paroxetine 20 mg/day. A group of patients (n=86) on duloxetine 40 mg/day was also included in this study but since antidepressant effects of this group were not significantly different from placebo, the tolerance data is not included here.

SNRIs=serotonin and norepinephrine reuptake inhibitors; SSRIs=selective serotonin reuptake inhibitors; IR=immediate release; XR=extended release.

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sexes, is related to serotonergic stimulation of 5-HT₂ and 5-HT₃ receptors but has a complex origin probably also involving the effect of 5-HT on nitric oxide production as well as other systems.¹²³

Therefore, it is not unexpected that venlafaxine, which has a major serotonergic component, also produces considerable sexual dysfunction. An observational study conducted in >1,000 US primary care clinics involving >6,000 patients¹²⁴ found the prevalence of sexual dysfunction, as measured by the Changes in Sexual Functioning Questionnaire, associated with SSRIs and venlafaxine to be similar with rates ranging from 36% to 43%.

Data for the occurrence of sexual dysfunction has not been reported with milnacipran but Deakin and Dursan¹²⁵ have estimated the prevalence to be lower with milnacipran than with venlafaxine and much lower than with the SSRIs.

In a study comparing paroxetine and duloxetine,¹²⁶ 70% of the patients had sexual dysfunction at baseline as judged by Arizona Sexual Experience Scale criteria. Among patients without sexual dysfunction at baseline, 29% of those receiving duloxetine and 35% of those receiving paroxetine complained of sexual dysfunction at endpoint compared with 17% on placebo.⁷⁰ In a second study,⁶⁷ the incidence of treatment-emergent sexual side effects was 46.5% for duloxetine and 62.8% for paroxetine. None of these differences were significant. In a 1-year open-label study with duloxetine,¹²¹ adverse events related to sexual dysfunction included decreased libido (4.1%), ejaculation failure (2.7%), and erectile dysfunction (2.5%), suggesting that, at least qualitatively, the problems are the same as those seen with the SSRIs.

Withdrawal Effects

Several SSRIs, in particular paroxetine, have been reported to produce a number of posttreatment emergent adverse events following abrupt withdrawal sometimes known as 5-HT withdrawal syndrome.¹²⁷⁻¹²⁹ Anecdotal evidence^{130,131} suggests that venlafaxine can cause similar problems. It appears, however, that this is not necessarily true for the whole of the SNRI class. A post hoc analysis of patients abruptly withdrawn from paroxetine and milnacipran as part of a double-blind comparative protocol¹³² showed that when given under identical conditions at equally effective doses, paroxetine produced significantly more posttreatment-emergent adverse events than milnacipran. This was true after both a relatively short course of treatment (6 weeks) and a longer (24 week) treatment period. In addition, the qualitative nature of the adverse events differed between the two drugs, with the classical

symptoms of dizziness, anxiety and sleep disturbance (insomnia and nightmares) as the principal effects occurring with paroxetine, while increased anxiety was the only effect reported with milnacipran.

No data are yet available on duloxetine. It is possible that the balance between serotonergic and noradrenergic neurotransmission may play an important role in determining the nature and extent of withdrawal-related symptoms.

Cardiovascular Effects

Stimulation of catecholamine neurotransmission, noradrenergic, and, possibly, especially in the case of overdose with venlafaxine, the dopaminergic systems has a theoretical potential for increasing blood pressure.

Venlafaxine can cause clinically significant increases in blood pressure¹³³ in some patients and regular monitoring of blood pressure throughout venlafaxine therapy is recommended in the prescribing information. A pooled analysis of placebo-controlled studies¹³³ showed that, overall, venlafaxine has a low incidence of clinically significant increases in blood pressure at doses <200 mg/day. However, 5.5% of patients treated with doses >200 mg/day showed clinically relevant sustained hypertensive effects. In patients treated with venlafaxine 300–375 mg/day, the mean increase in diastolic blood pressure was 7 mm Hg.¹³³ A meta-analysis of original data on blood pressure using data from 3,744 patients¹³⁴ concluded that venlafaxine treatment showed dose-dependent increases in supine diastolic blood pressure but that clinically significant hypertension is only induced at doses >300 mg/day.

Studies in guinea pigs¹³⁵ have shown that venlafaxine may cause direct cardiac electrophysiological effects by inhibiting the inward sodium current in ventricular myocytes. At high doses, this could cause QRS prolongation, seizures, tachycardia, and proarrhythmic effects. Indeed, in overdose, following the ingestion of venlafaxine 3 g, cardiac rhythm disturbances have been reported including an increase of QTc.¹³⁶

Because of concerns about potential problems of blood pressure and cardiotoxicity, the United Kingdom's Committee for the Safety of Medicines¹³⁷ has recently recommended that venlafaxine should not be used in patients with a history of cardiac failure, coronary artery disease or electrocardiogram (ECG) abnormalities, patients with electrolyte imbalance or in patients who are hypertensive.

Blood pressure increases with milnacipran are minimal. A study comparing milnacipran 100 mg/day and milnacipran 200 mg/day with fluoxetine 20 mg/day¹³⁸ found no change in blood pressure. Tachycardia (defined as a heart rate of >100 beats per minute [BPM]), how-

ever, was seen in 3% of patients on milnacipran 100 mg/day and 6% of patients on milnacipran 200 mg/day. A study comparing milnacipran and fluvoxamine⁶⁵ reported hypertension (not defined) in 3.5% of patients on milnacipran 100 mg/day but no tachycardia. A review of over 4,000 patients treated with milnacipran⁴⁴ showed that the mean increase in blood pressure was <1 mmHg while the mean increase in heart rate was 3.6 BPM. An examination of 1,253 ECGs of patients taking milnacipran showed a change of QTc of -1.7 msec compared with +3.9 msec for patients treated with TCAs. Consistent with this, no cardiotoxicity has been reported in overdose of up to 28 times the recommended daily dose.¹³⁹

Duloxetine does not appear to be associated with sustained hypertension. Pooled data of 735 patients taking duloxetine 40–120 mg/day¹⁴⁰ showed that only 0.7% of patients had a 10 mmHg increase in systolic or diastolic blood pressure compared with 0.4% of patients on placebo. Heart rate was increased by <1 BPM. No effect on QTc interval was observed compared with a 4.7 msec increase with venlafaxine and 1.9 msec decrease with placebo. A recent meta-analysis of indices of cardiovascular safety¹⁴¹ showed small but significant increases in heart rate and systolic blood pressure compared with placebo but these were similar to the effects seen with the comparators, fluoxetine and paroxetine. Mean changes with duloxetine in ECG (QTc, PR, and QRS intervals) were neither clinically nor statistically significant.

SNRIs in Overdose

Accidental drug overdose is not uncommon especially in the elderly. In addition, nearly 50% suicide attempts involve a drug overdose and in ~14% of cases, the prescribed antidepressant is implicated.¹⁴² Therefore, safety in overdose is a legitimate concern with all antidepressants.

It is clear that the introduction of the more recent generations of antidepressants, SSRIs and SNRIs, has been accompanied with a significant gain in safety in overdose compared with the TCAs,¹⁴³ resulting in significantly less fatalities and these usually only involving multi-compound ingestion.

A recent analysis of 469 cases of SSRI overdose¹⁴⁴ found that SSRIs were relatively safe in overdose. Nevertheless, seizures and coma occurred in 1.9% and 2.4% cases, respectively, while the incidence of serotonin syndrome was 14%. Overdoses with citalopram resulted in significant prolongation of QTc (>440 msec) in 68% of cases. SSRIs are rarely fatal when taken alone¹⁴² but deaths occur more frequently following serotonin syndrome induced by SSRIs in combination with other compounds, especially monoamine oxidase inhibitors, such as moclobemide.¹⁴⁵

Overdose with venlafaxine can be associated with sedation, sinus tachycardia, seizures, hypotension, hypertension, diaphoresis, hyponatremia, and serotonin syndrome.^{146,147} Cardiac rhythm disturbances, including an increase of QTc leading to atrial fibrillation, have also been reported.¹³³ As with TCAs, these effects can be reversed by the infusion of sodium bicarbonate.¹³³ Fatalities have been reported due to overdose of venlafaxine alone or in combination with other compounds^{148,149} often following serotonin syndrome. A comparative study of the effects of venlafaxine and citalopram in overdose¹⁵⁰ concluded that citalopram was more likely to cause QT prolongation, while venlafaxine caused more frequent features of the 5-HT syndrome. Both citalopram and venlafaxine were proconvulsants.

Fatal toxicity index (deaths caused by a drug/million prescriptions) is a very crude measure of drug toxicity. It does not take into account important factors, such as the differences in population. SSRIs, for example, are used principally as first-line treatment in mildly depressed patients, whereas venlafaxine is often used in more severely depressed resistant and more suicidal patients. Nevertheless, these data provide some important indications. Deaths in England, Scotland, and Wales due to acute poisoning by a single antidepressant, with or without ingestion of alcohol, have been compiled for the period 1993–1999.¹⁵¹ While TCAs, such as diethazine and amitriptyline, had fatal toxicity indexes of 53 and 38 deaths/million prescriptions, respectively, the SSRIs caused 1–3 deaths/million prescriptions. In contrast, venlafaxine had an index of >13 deaths /million prescriptions. A subsequent analysis for the period 1998–2000¹⁵² produced similar results for the SSRIs and venlafaxine (1–3 and 13 deaths/million prescriptions, respectively). Therefore, it seems that venlafaxine is considerably more dangerous in overdose than the SSRIs. These data have led UK's Medicine and Healthcare Products Regulatory Agency¹⁵³ to limit the use of venlafaxine to second-line only and to restrict its prescriptions to mental health specialists. Milnacipran appears not to cause any particular problems in overdose. Patients have absorbed up to 2.8 g (1 month's supply at the recommended dose) without any major effects other than sedation. In particular, no cardiovascular complications have been recorded. No fatalities have been recorded with milnacipran.¹³⁹ At the present time, no cases of overdose with duloxetine have been published.

CONCLUSION

Although the SNRIs now comprises three members—venlafaxine, milnacipran, and duloxetine—the majority of data have been generated with venlafaxine.

Hence, there is a risk that the properties of venlafaxine will be associated with the class as a whole. From the limited data available for the two other SNRIs, there appears to be significant differences in their profiles and such a gross classification may prove to be erroneous.

In terms of antidepressant activity, data with venlafaxine tend to suggest that treatment with SNRIs results in higher rates of response and, particularly, remission than single-action antidepressants, such as SSRIs. This tendency is supported by evidence with milnacipran and to a lesser extent with duloxetine. Studies with other dual-action antidepressants, such as TCAs, mirtazapine,¹⁵⁴ and even ad hoc dual-action combinations of selective compounds,⁵ are also consistent with this hypothesis. Nevertheless, it is prudent to bear in mind that this conclusion is based principally on studies comparing a single SNRI, venlafaxine, and two SSRIs (fluoxetine, and paroxetine). Individual studies with other SSRIs, such as citalopram and sertraline, suggest that the conclusions may need to be refined when more data are available on individual compounds.

Although "response" (usually defined as a decrease of at least 50% of the baseline score on a depression rating scale) is often used as an outcome measure in antidepressant trials, it is not an acceptable outcome in clinical practice. Seriously ill patients with a high baseline score can have a 50% reduction in symptoms but be left with significant residual symptoms.¹⁵⁵ Such symptoms not only seriously affect the quality of life of the patient but also indicate the continuation of the depressive episode with the risk of it developing into a new episode. Patients with residual symptoms have been found to be three times more likely to relapse than patients in full remission without residual symptoms.¹⁵⁶ The aim of modern antidepressant therapy should be full, sustained remission. To obtain this, it is important to have available drugs that act on all of the symptoms associated with depression, including somatic symptoms and pain.

Although there are one or two exceptions, most studies have shown SSRIs to be ineffective in the treatment of neuropathic pain and painful symptoms associated with depression. In contrast, there is evidence from all three SNRIs that this class is helpful in relieving chronic pain both associated with and independent of depression. Since pain is increasingly being seen as an integral part of depression⁹⁷ the availability of antidepressants capable of acting on all of the symptoms of depression, including somatic symptoms and pain, is a significant advancement.

The majority of depressed patients also suffer

from one or more anxiety disorders. In common with SSRIs, SNRIs seem to be efficacious in most anxiety disorders, although data are still sporadic for some. There do not appear to be major differences between the two classes in terms of efficacy in anxiety disorders but comparative data are still sparse. Qualitative, rather than quantitative, differences may be more likely with certain categories of patients being more responsive to one class or another.

Tolerability of the SNRIs at therapeutic doses is one of the most variable parameters within the class. At doses necessary to produce a superior efficacy to the SSRIs, venlafaxine is less well-tolerated than the selective agents. It combines the principal adverse effects of the SSRIs (nausea, sexual dysfunction, withdrawal problems) with dose-dependent cardiovascular phenomena (principally increased blood pressure). Although no direct comparative data exist between the SNRIs, not all of the adverse effects seen with venlafaxine appear to be as common for the rest of the class. Although nausea is the most common adverse effect for all three SNRIs, on the basis of current data the risk of treatment-emergent increases in blood pressure appear to be greater for venlafaxine than with duloxetine or milnacipran.

Toxicity in overdose is a legitimate concern with any psychotropic drug, especially with antidepressants. Although fatal toxicity index is a very crude analysis, it does indicate that venlafaxine is possibly more dangerous in overdose than the SSRIs. The apparent greater cardiotoxicity with venlafaxine suggest that the toxicity in overdose is probably specific to venlafaxine itself and is not a class phenomenon. Unfortunately, at this time, insufficient data are available with milnacipran or duloxetine to confirm this hypothesis.

Thus, SNRIs represent a class of compounds apparently capable of treating the whole gamut of depressive symptomatology and in doing so are capable of producing remission in a greater proportion of treated patients. Neurochemically, the three compounds show differing selectivities for the reuptake of 5-HT and NE. It is likely that their clinical profiles will reflect this. Comparative studies within the SNRI class are required to further document this possibility. In particular, it is important to determine whether the advantages of the class are necessarily associated with a reduced tolerability in overdose as seen with venlafaxine or whether with milnacipran and/or duloxetine it is possible to win on both the swings and the roundabout and benefit from increased efficacy and good tolerability. **CNS**

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