Open Journal of Depression
2013. Vol.2, No.4, 54-63
Published Online November 2013 in SciRes (http://www.scirp.org/journal/ojd)

Scientific Research
http://dx.doi.org/10.4236/ojd.2013.24011

A Review of the Serotonin-Norepinephrine Reuptake Inhibitors: Pharmacologic Aspects and Clinical Implications for Treatment of Major Depressive Disorder and Associated Painful Physical Symptoms*

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Received July 16th, 2013; revised August 20th, 2013; accepted September 1st, 2013

Background: Depression is characterized by low mood, low self-esteem, and loss of interest or pleasure. Painful physical symptoms (PPS) associated with depression have a negative impact on the probability of remission. Because both norepinephrine and serotonin are involved with the central regulation of pain, the serotonin-norepinephrine reuptake inhibitors (SNRIs) may have more success than the selective serotonin reuptake inhibitors (SSRIs) in impacting PPS as well as the core emotional symptoms of depression. **Methods:** Published preclinical and clinical data on the SNRIs (i.e., milnacipran, venlafaxine, and duloxetine) have been reviewed, paying special attention to the differentiation of the pharmacological aspects of the SNRIs. The efficacy and safety results on depression and associated PPS have also been summarized. **Results:** Each of the SNRIs has different profiles regarding the inhibition of binding to human serotonin and norepinephrine uptake transporters and clinical pharmacokinetics. All SNRIs have data for alleviating the core symptoms of depression; duloxetine and venlafaxine show efficacy for PPS associated with depression. There are also differences in tolerability and adverse events profiles. **Conclusions:** Although all SNRIs have the same dual mechanism of action for the treatment of depression, they have different pharmacologic profiles that may impact clinical outcomes.

Keywords: Duloxetine; Venlafaxine; Milnacipran; Serotonin-Norepinephrine Reuptake Inhibitors; Painful Physical Symptoms; Major Depressive Disorder

Introduction

The core symptoms of major depressive disorder (MDD) include depressed mood or the loss of interest or pleasure in nearly all activities, as well as changes in appetite, sleep or psychomotor activity, decreased energy, feelings of worthlessness or guilt, difficulty concentrating or making decisions, and suicidality. Just as important, however, are the associated symptoms (including tearfulness, irritability, brooding, obsessive rumination, anxiety, phobias, pain, and sexual dysfunction) (APA, 2000). Given the profound impact of MDD on individuals and on society as a whole, the importance of the treatment of this disorder is difficult to overstate.

After the development of the tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) were an important milestone in the pharmacological treatment of MDD. During the SSRIs era, there was renewed interest in the combined roles of norepinephrine (NE) and serotonin (5 HT) in depression. Neurotransmitter depletion studies demonstrate that both 5-HT and NE are independently involved in the pathophysiology of depression (Delgado et al., 1990; Delgado et al., 1993; Delgado, Moreno, Potter, & Gelenbert, 1997), and there is evidence that blocking the reuptake of both may result in increased efficacy (Danish University Antidepressant Group, 1986; Danish University Antidepressant Group, 1990; Nelson, Mazure, Jatlow, Bowers, & Price, 2004). Along with this shift, there was a new focus on painful physical symptoms (PPS), which are frequently associated with depression and are an important factor in treatment outcome (Leuchter et al., 2010).

Serotonin-norepinephrine reuptake inhibitors (SNRIs), with their selective effects on both 5-HT and NE, may provide both greater efficacy and increased convenience of a single agent for the treatment of depression and associated painful symptoms. Development of these newer antidepressants represents an important advance in the standard treatment of depression, by virtue of treating a broader range of symptoms associated with MDD.

*Disclosure of interests: Drs. Alev, Lenox-Smith, Altin, and Dueñas are employees and minor stockholders of Eli Lilly and Company.
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The Link between Painful Physical Symptoms and Depression

Beyond the core diagnostic criteria of depression, there are symptoms associated with depression that are not unique to MDD (APA, 2000). In a literature review of 14 studies that examined the prevalence of pain among patients with depression (in a mix of primary care and psychiatric settings), the mean prevalence of pain was 65%, with a range from 15% to 100% (Bair, Robinson, Katon, & Kroenke, 2003). More recently, a United States study (A Randomized Trial Investigating SSRI Treatment [ARTIST]) conducted in 573 patients with depression reported that more than two-thirds (69%) of the patients complained of pain symptoms of mild severity or above (Bair et al., 2004). In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, 80% of the participants complained of PPS (Leuchter et al., 2010).

Studies have also shown that the presence of PPS makes the treatment of depressed patients more difficult. Patients with moderate to severe pain at baseline were 2 to 4 times as likely to experience poor depression response and health-related quality of life after 3 months of treatment compared with patients with no pain (Bair et al., 2004).

Following treatment with an SSRI antidepressant, although mood symptoms of depression were improved, physical symptoms, PPS in particular, were more likely to persist (Greco, Eckert, & Kroenke, 2004). Also, patients with severe pain at baseline were less likely to achieve remission than those with no pain at baseline (odds ratio [OR] = .11, 95% confidence interval [CI] .05 to .25) and patients whose pain improved early on were more likely to achieve remission (OR = .90, 95% CI 1.03 to 3.49) (DeVeaugh-Geiss et al., 2010). Finally, Leuchter et al. (2010) found PPS to be a possible indicator of poorer treatment outcome for MDD when an initial SSRI was used. Thus, when painful symptoms and depression are both present, recovery takes longer and is less likely.

Neurobiology of the Norepinephrine and Serotonin Pathways and Their Roles in Pain Regulation

Both 5-HT and NE neurons have ascending tracts to the cerebral cortex and limbic area, but have descending tracts to the spinal cord as well (Fields, Heinricher, & Mason, 1991). Serotonergic neurons in the rostral ventromedial medulla act on various receptor subtypes to exert complex modulatory effects on nociceptive transmission in the dorsal horn (**Table 1**). Antinociceptive effects occur when 5 HT1A receptors inhibit excitability of spinothalamic neurons and excitatory interneurons and presynaptic $5\text{-HT}_{1B/D}$ receptors inhibit neurotransmitter release from primary afferents. Descending serotonergic pathways also have pronociceptive effects. Stimulation of 5-HT_2 receptors increases excitability of postsynaptic spinothalamic neurons. Also, 5-HT_3 receptors (cation channels that elicit depolarization) act presynaptically to increase neurotransmitter release from primary nociceptive afferents and postsynaptically to increase excitability of spinothalamic neurons (Benarroch, 2008). Thus, the descending 5-HT pathways may exert either inhibitory or excitatory effects on pain perception.

Noradrenergic neurons in the pontine tegmentum also project to the dorsal horn, where they produce mostly antinociceptive effects. Norepinephrine primarily inhibits nociceptive transmission in the dorsal horn via presynaptic α_2 receptors in primary nociceptive terminals. These receptors may also mediate postsynaptic inhibition of spinothalamic neurons. Activation of postsynaptic α_1 receptors may contribute to antinociception by increasing the release of γ-aminobutyric acid (GABA) or glycine by local inhibitory neurons (Benarroch, 2008). Thus, 5-HT and NE function as part of the body's endogenous analgesic system but may become dysfunctional in depression and lead to PPS (Stahl, 2002).

Table 1.
Summary of nociceptive and antinociceptive actions of serotonin and norepinephrine in the dorsal horn of the spinal cord.

Receptor	Action	Target	Effect
5-HT			
5-HT_{1A}	Postsynaptic inhibition	STNs	↓ Pain
5-HT_{1A}	Postsynaptic inhibition	Excitatoryinterneurons	↓ Pain
$5\text{-HT}_{1B/D}$	Inhibit NT release	Primary afferents	↓ Pain
5-HT_2	Postsynaptic excitation	STNs	↑ Pain
5-HT_3	Increase NT release	Primary afferents	↑ Pain
5-HT_3	Postsynaptic excitation	STNs	↑ Pain
NE			
α_2	Inhibit NT release	Primary afferents	↓ Pain
α_2	Postsynaptic inhibition	STNs	↓ Pain
α_1	Postsynaptic excitation	Inhibitory Interneuron	↓ Pain

Abbreviations: 5-HT = serotonin, NE = norepinephrine, NT = neurotransmitter, STNs = spinothalamic neurons.

In this review, we report findings of a literature search of the preclinical and clinical data of the SNRIs, specifically duloxetine, milnacipran, and venlafaxine. Preclinical data focus mainly on pharmacologic aspects and differentiation between the SNRIs. Clinical study results are evaluated with regard to efficacy and safety/tolerability in the treatment of MDD. Both acute and long-term, placebo-controlled or active comparator studies are considered. Separately, efficacy results are reviewed with regard to MDD and associated PPS. In addition, we attempt to provide information about the connection between pharmacologic profile and clinical outcome.

Pharmacological Aspects of the Serotonin-Norepinephrine Reuptake Inhibitors

Preclinical Data: Reuptake Inhibition of Serotonin and Norepinephrine

By definition, all SNRIs block the reuptake of both 5-HT and NE, but the potency and balance of this reuptake inhibition may help determine their different clinical properties. **Table 2** lists the inhibition constants (K_i, nM) for inhibition of binding to human NE and 5-HT uptake transporters for the SNRIs (and a selection of SSRIs and TCAs for comparison). The NE/5-HT ratio of K_i's is provided as a measure of the balance of the inhibition of the reuptake of these 2 neurotransmitters. Duloxetine is a potent (low K_i) and relatively balanced (ratio near 1)

Table 2.
Inhibition of binding to human monoamine uptake transporters (K_i, nM).

Drug	NE Transporter[a] K_i, nM	5-HT Transporter[a] K_i, nM	NE/5-HT Ratio[b] (1 = balance)
SNRIs			
Duloxetine[c]	7.5	.8	9.4
Venlafaxine[c]	2480	82	30
Milnacipran[d]	200	123	1.6
SSRIs			
Fluoxetine[e]	1021	6.9	148
Paroxetine[e]	132	.38	330
Sertraline[d]	715	.9	794
Citalopram[e]	>10000	9.5	>1053
Tricyclics			
Clomipramine[f]	38	.28	136
Desipramine[d]	3.8	179	.02

[a]The lower the number, the larger potency or affinity for transporter inhibition. [b]A ratio >1 indicates 5-HT is inhibited to a greater extent than NE. [c]Bymaster et al. (2001) *Neuropsychopharmacology*, 25, 871-880. [d]Koch et al. (2003) *Neuropharmacology*, 45, 935-944. [e]Koch et al. (2002) *Neuropsychopharmacology*, 27, 949-59. [f]Tatsumi et al. European Journal of Pharmacology, 340, 249-258. Abbreviations: 5-HT = serotonin, NE = norepinephrine, SNRI = serotonin-norepinephrine reuptake inhibitors, SSRI = selective serotonin reuptake inhibitors.

5-HT/NE reuptake inhibitor. However, because of the higher NE/5-HT ratio of venlafaxine, the NE reuptake properties of this agent are generally not evident until a dose of at least 150 mg/day is achieved (Wong & Bymaster, 2002). Evidence for this comes from microdialysis experiments in rats showing the dose required to block NE depletion by 50% (ED_{50}) is 14.9 mg/kg for duloxetine compared with >100 mg/kg for venlafaxine (Iyengar, Webster, Hemrick-Luecke, Xu, & Simmons, 2004).

Davidson et al. (2005) found that venlafaxine (extended release) at a dose of 225 mg/day produced 56% NE transporter occupancy using an *ex vivo* method. Kihara and Ikeda (Kihara & Ikeda, 1995) also showed using microdialysis that duloxetine administration in rats results in balanced increases in 5-HT and NE even at the lowest doses (without having to "push" the dose). Milnacipran is an even more balanced 5-HT/NE reuptake inhibitor, but is less potent, as evidenced by its NE and 5-HT transporter K_i's.

In addition to NE and 5-HT, duloxetine is a weak inhibitor of dopamine reuptake. However, it has no significant affinity for dopaminergic, cholinergic, histaminergic, adrenergic, opioid, glutamate, or GABA receptors *in vitro* and does not inhibit monoamine oxidase (Knadler, Lobo, Chappel, & Bergstrom, 2011). Venlafaxine is also a weak inhibitor of dopamine reuptake but has no significant affinity for muscarinic cholinergic, H_1-histaminergic, or α_1-adrenergic receptors *in vitro* (Wyeth Pharmaceuticals, Inc, 2012). Milnacipran has a mild affinity for N methyl-D-aspartate receptors. However, it has no significant affinity for serotonergic ($5\text{-}HT_{1\text{-}7}$), α- and β-adrenergic, muscarinic ($M_{1\text{-}5}$), histamine ($H_{1\text{-}4}$), dopamine ($D_{1\text{-}5}$), opiate, benzodiazepine, and GABA receptors *in vitro* (English, Rey, & Rufin, 2010).

Clinical Pharmacokinetics

Clinical pharmacokinetic information for milnacipran, venlafaxine, and duloxetine is provided in **Table 3**.

Because milnacipran, venlafaxine, and duloxetine are all at least partially excreted through the urine, their use should be carefully considered in patients with renal impairment. For patients with severe renal impairment, a reduced dose of milnacipran is recommended. Milnacipran is not recommended in patients with end-stage renal disease. Dose reduction of venlafaxine is recommended for patients with renal impairment and patients undergoing dialysis. Duloxetine is not recommended for patients with severe renal impairment or end-stage renal disease.

In terms of hepatic metabolism, milnacipran is not metabolized by cytochrome P450 enzymes (and no dosage adjustment is necessary for patients with hepatic impairment) (Forest Laboratories, Inc, 2012), but venlafaxine (Wyeth Pharmaceuticals, Inc, 2012) and duloxetine (Eli Lilly and Company, 2012; Nelson et al., 2004) are. Patients with hepatic insufficiency have decreased duloxetine metabolism and elimination; therefore, duloxetine should ordinarily not be used in patients with this condition (Eli Lilly and Company, 2012; Nelson et al., 2004). Duloxetine is a cytochrome P450 2D6 (CYP2D6) inhibitor, which may result in various drug interactions (Eli Lilly and Company, 2012; Nelson et al., 2004). Venlafaxine is also metabolized in the liver, so dosage adjustment is necessary in hepatically impaired patients (Wyeth Pharmaceuticals, Inc, 2012). Venlafaxine is unique among the SNRIs in that it's therapeutic properties are thought to be primarily the result of its metabolite, O-desmethylvenlafaxine. Metabolism of venlafaxine into O desmethylvenlafaxine occurs in the liver principally by CYP2D6 (Lobello et al., 2010)].

Efficacy in the Treatment of Depression and Associated Painful Physical Symptoms

In the following section, we will review the efficacy of the SNRIs in their treatment of MDD and associated PPS.

Milnacipran

Two clinical trials comparing milnacipran with placebo have been summarized by Lecrubier et al. (1996). Study 1 was an 8-week, dose-ranging study of outpatients with moderate/severe depression (Hamilton Depression Rating Scale [HAMD] 17-item [HAMD-17] total score >22). Both the 50-mg and 100-mg doses, but not the 25-mg dose, of milnacipran resulted in significant improvement on the HAMD-17 and Montgomery-Åsberg Depression Rating Scale (MADRS) compared with placebo. Study 2 was carried out in hospitalized patients with HAMD-17 scores ≥22. Significant improvement was found on the HAMD-17 (change from baseline, milnacipran −51%, placebo −38%; $p < .05$), but not the MADRS or the Clinical Global Impressions (CGI) scale. In a placebo-controlled, relapse-prevention study, milnacipran (50 mg twice daily) was superior to placebo in the prevention of relapse in patients who had responded to acute treatment and had remained in remission during a 4-month continuation phase (Rouillon et al., 2000a; Rouillon, Warner, Pezous, & Bisserbe, 2000b).

A number of clinical trials have compared milnacipran with SSRIs. In a 6-week, double-blind comparison, fluoxetine (20 mg/day) exhibited better efficacy than milnacipran

Table 3.
Pharmacokinetic properties of milnacipran, venlafaxine, and duloxetine.

	Milnacipran[a]	Venlafaxine XR[b]	Duloxetine[c]
Absorption and Distribution			
Absolute bioavailability	85% - 90%	45%	43%[d]
T_{max}	2 - 4 hours	5.5 (Ven), 9 (ODV) hours	6 - 10 hours
Plasma protein binding	13%	27% (Ven), 30% (ODV)	>90%
Time to steady-state level	36 - 48 hours	Within 3 days	Within 3 days
Terminal elimination half-life	6 - 8 hours	5 ± 2 (Ven), 11 ± 2 (ODV) hours	8 - 17 hours
Metabolism and Elimination			
Active metabolite	None	ODV	None
Main metabolism	Glucuronidation	Hepatic	Hepatic
Excretion in urine	55% (unchanged)	87%	70%

[a]Savella package insert (Forest Laboratories, Inc, 2012). [b]Effexor XR package insert (Wyeth Pharmaceuticals, Inc, 2012). [c]Cymbalta package insert (Eli Lilly and Company, 2012). [d]Lobo, E.D. et al. (2008) *Clinical Pharmacokinetics*, 47, 191-202. Abbreviations: T_{max} = time to peak concentration, Ven = venlafaxine, ODV = O-desmethylvenlafaxine.

(100 mg/day) on the MADRS, HAMD, CGI-Severity (CGI-S) (Ansseau et al., 1994). However, the lower efficacy of milnacipran was possibly because milnacipran, which possesses an elimination half-life of 6 to 8 hours, was given only once daily. A similar study that used a split dose for milnacipran found no significant difference in efficacy between milnacipran and fluoxetine, though a significant increase in heart rate (HR) was noted for milnacipran (Guelfi et al., 1998). In a comparison with fluvoxamine (100 mg twice daily), milnacipran (50 mg twice daily, 6 weeks) produced a significantly greater reduction in MADRS scores and a higher response rate (decrease of 50% or more of the MADRS score from baseline; milnacipran = 78.9%; fluvoxamine = 60.7%) (Clerc, 2001). Comparisons of milnacipran with paroxetine have shown the 2 antidepressants have equivalent efficacy in diverse populations (Chang et al., 2008; Lee et al., 2005; Sechter et al., 2004). A meta-analysis showed that there were no differences in clinical improvement, remission, or overall tolerability when comparing milnacipran with SSRIs (Nakagawa et al., 2008).

Little research has been done on the efficacy of milnacipran in the treatment of PPS associated with depression. However, the efficacy of milnacipran in patients with fibromyalgia has been well-established, and milnacipran has been approved for this indication by the United States Food and Drug Administration (FDA) based on 2 pivotal clinical trials (Clauw, Mease, Palmer, Gendreau, & Wang, 2008; Mease et al., 2009).

Venlafaxine

The efficacy of venlafaxine has been established in several placebo-controlled trials, often including an SSRI comparator. Nemeroff and Thase (2007) found that venlafaxine (75 to 225 mg/day) was superior to placebo (but not to fluoxetine [20 to 60 mg/day]). Shelton et al. (2005) pooled results from 5 active, placebo-controlled studies and found that the response rate for venlafaxine was significantly greater than placebo or fluoxetine/paroxetine. However, Schatzberg and Roose (2006) found, in a placebo-controlled comparison of venlafaxine and fluoxetine, that all 3 groups improved significantly on the HAMD 21-item (HAMD-21) after 8 weeks of treatment, but that there were no significant differences among the treatment groups on the change in HAMD-21, MADRS, or CGI scores. Finally, a relapse-prevention study has shown that relapse rates were significantly lower for treatment with venlafaxine than with placebo after 2 years (28.5% vs. 47.3%, $p = .005$) (Kornstein, 2008).

Venlafaxine has been compared with SSRI antidepressants in several meta-analyses. Meta-analyses (or pooled analyses) are useful because individual trials are not usually powered to demonstrate differences between antidepressants. Thase et al. (2001) found that remission rates for venlafaxine were significantly higher than for SSRIs (45% versus 35%, respectively; $p < .001$, number needed to treat [NNT] = 10). Smith et al. (2002) also found an advantage for venlafaxine over the SSRIs (effect size= −.17, 95% CI= −.27 to −.08). Papakostas et al. (2007) showed the pooled response rates for venlafaxine to be somewhat greater than rates for the SSRIs (68% versus 61.2%, respectively). Finally, Nemeroff et al. (2008) found the overall difference in remission rates between venlafaxine and SSRIs was 5.9% favoring venlafaxine ($p < .001$, NNT = 17).

Genetic factors may contribute to individual variations in efficacy with SNRIs. Venlafaxine is metabolized primarily by the highly polymorphic enzyme cytochrome P450 2D6 to yield the pharmacologically active metabolite O-desmethylvenlafaxine. As there is variability in the population with regard to the efficiency of this enzyme, up to 10% of Caucasians will not receive the full effect of venlafaxine (Lobello et al., 2010; Zanger, Raimundo, & Eichelbaum, 2004). Lobello et al. (2010) found a significantly higher percentage of extensive metabolizers achieved response or remission compared with poor metabolizers, but found no differences in tolerability. Given duloxetine is mainly metabolized via cytochrome P450 1A2, it would be expected that duloxetine metabolism would not be affected, thus efficacy would also be unaffected. This finding could help explain duloxetine-related improvement in depressive symptoms in patients switching from venlafaxine because of suboptimal response (Wohlreich et al., 2005).

Studies with venlafaxine in adults also have established efficacy in the reduction of PPS related to depression, though these studies were of open-label design. Plesnicar (2010) found a response rate of 93% (50% reduction of HAMD-17 score from baseline) and an overall statistically significant improvement on the Depression and Somatic Symptom Scale (33.6 versus 12.4, $p < .0001$) after 8 weeks of treatment with venlafaxine (75 to

375 mg/day). Bradley et al. (2003) found, after 12 months of treatment with venlafaxine (≥150 mg/day), that HAMD-21 scores and visual analogue scale (VAS) scores for pain had decreased significantly from baseline. Similar results have been noted in the elderly. Ibor et al. (2008) found a response rate of 81.6% (as defined by a ≥50% decrease in HAMD-17 score) and significant improvement on the VAS for pain ($p < .0001$) after 24 weeks of treatment with venlafaxine (75 to 225 mg/day) in patients older than 60 years of age.

There is a question about whether venlafaxine functions mostly as an SSRI at the lowest dosages. For example, venlafaxine (75 mg) does not potentiate the NE-mediated venoconstrictor response, whereas a higher dose (150 mg) does (Abdelmawla, Langley, Szabadi, & Bradshaw, 1999). This may help explain venlafaxine's increased efficacy at higher doses. Rudolph et al. (1998) studied 3 dosages (75, 225, and 375 mg/day) and found that the dose-response relationship between venlafaxine and HAMD-21 total score at Week 6 was statistically significant ($p \leq .01$).

Duloxetine

The efficacy of duloxetine has been established in several placebo-controlled, randomized trials (Brannan et al., 2005; Detke, Lu, Goldstein, McNamara, & Demitrack, 2002; Detke, Lu, Goldstein, Hayes, & Demitrack, 2002; Goldstein, Mallinckrodt, Lu, & Demitrack, 2002; Mallinckrodt et al., 2003; Nemeroff et al., 2002; Nierenberg et al., 2007; Perahia et al., 2006; Raskin et al., 2007). Data from 4 randomized, double-blind, placebo-controlled trials of duloxetine 60 mg once daily were pooled for an analysis of the efficacy of duloxetine versus placebo in MDD treatment (Shelton et al., 2007). Duloxetine has also been shown to be effective in the prevention of relapse of MDD. In a re-analysis of a relapse-prevention study (Perahia et al., 2009), Kelin et al. (2010) found that, considering only patients taking 60 mg/day duloxetine, during the double-blind maintenance phase (up to 52 weeks), 31.7% of placebo-treated patients experienced a depressive recurrence, compared with 12.5% of duloxetine-treated patients ($p = .004$).

Duloxetine has been compared with fluoxetine and paroxetine in 6 clinical trials. In a pooled analysis of those trials, rates of remission (defined as a HAMD-17 total score ≤7) for the active treatments were significantly greater than placebo, but were not significantly different from each other (duloxetine 40.3%, SSRIs 38.3%, placebo 28.4%). However, a subanalysis of patients with moderate/severe depression (defined as a HAMD-17 total score ≥19) showed duloxetine to be superior to the 2 SSRIs in this group (35.9% versus 28.6%; $p < .046$) (Thase et al., 2007). Another meta-analysis showed the pooled response rates to duloxetine and SSRIs to be virtually identical (51.6% versus 51.4%, respectively), though reasons to interpret this result with caution were cited (Papakostas et al., 2007). In an open-label study of patients who did not respond to initial treatment with an SSRI, more than half responded (≥50% decrease in HAMD-17 total score from baseline to endpoint) to treatment with duloxetine (Perahia, Quail, Desaiah, Corruble, & Fava, 2008b).

Duloxetine has also been shown to be effective in the treatment of PPS related to depression. Analysis of pooled data from 2 identical, but independent, placebo-controlled, 9-week trials showed that patients treated with duloxetine (60 mg/day) demonstrated significantly greater improvement in overall pain (as measured on the VAS) compared with those treated with placebo ($p = .016$) (Fava, Mallinckrodt, Detke, Watkin, & Wohlreich, 2004). Brecht et al. (2007) found that, compared with placebo, duloxetine (60 mg/day) significantly reduced pain and improved depression, with significant mean changes in Brief Pain Inventory (BPI)-Short Form average pain scores. However, Brannan et al. (2005) found that duloxetine-related improvements in BPI scores at endpoint, compared with placebo, only approached significance. Mean changes at endpoint in depression rating scales (HAMD-17 and CGI-S) also did not differ significantly between duloxetine (60 mg) and placebo treatment groups. A summary of pooled data from 3 clinical trials, however, found that, compared with placebo, duloxetine was associated with significant reduction in pain severity (Goldstein et al., 2004). Perahia et al. (2008b) found that patients who did not respond to initial treatment with an SSRI and were switched to duloxetine (60 mg/day) saw significant improvement in VAS overall pain scores.

Comparisons of the Serotonin-Norepinephrine Reuptake Inhibitors

Perahia et al. (2008a) found no significant difference between duloxetine (60 mg/day) and venlafaxine (150 mg/day) as measured by global benefit risk assessment (efficacy/adverse events [AEs]; −1.418 versus −1.079, $p = .217$) and no significant differences between the groups on the majority of efficacy measures. Nausea was the most common treatment-emergent adverse event (TEAE) for both drugs and was significantly higher with duloxetine compared with venlafaxine (43.6% versus 35.0%, $p < .05$). Significantly more venlafaxine-treated patients experienced sustained elevations of systolic blood pressure [BP] ($p = .047$). More recently, in a re-analysis of the data reported by Perahia and colleagues, duloxetine has been shown to be noninferior to venlafaxine (Lenox-Smith, Kelin, Brnabic, & Bradley, 2011). A meta-analysis comparing 12 antidepressants found an efficacy advantage for venlafaxine over duloxetine (OR = .77, 95% CI = .60 to .99), but no difference in efficacy between duloxetine and milnacipran (OR = .97, 95% CI = .69 to 1.38) or milnacipran and venlafaxine (OR = .79, 95% CI = .58 to 1.08) (Cipriani et al., 2009). However, weaknesses of this meta-analysis and doubts about its conclusions have been raised. For example, the analysis included data from treatment arms using subtherapeutic dosages of duloxetine and most of inferences about duloxetine were drawn from indirect comparisons (Lenox-Smith, D'yachkova, Deberdt, & Raskin, 2010).

Safety/Tolerability

Many SNRI-related AEs are predictable from their mode of action. Thus, one sees the SSRI-type AEs (5-HT effects) such as nausea, vomiting, dizziness, and sexual dysfunction, but also the NE events such as raised BP, HR, and sweating. Other events, such as QT intervals, are drug-specific.

Milnacipran

Tolerability and safety of milnacipran have been reviewed by Puech et al. (1997). Dropouts caused by AEs were 6.1% in the placebo group, 7.6% with milnacipran, 14.8% with TCAs, and 7.8% with SSRIs. For patients receiving milnacipran, the AEs noted with a frequency significantly greater than for patients

receiving placebo were vertigo (5.0%), increased sweating (4.3%), anxiety (4.1%), hot flushes (3.0%), and dysuria (2.1%). Treatment with milnacipran resulted in a mild increase in HR (3.2 beats per minute [bpm]) and a negligible effect on BP (<1 mmHg). In contrast, there was an increased incidence of orthostatic hypotension (defined as a decrease of >20 mmHg) with milnacipran (21%). Milnacipran had minimal effects on the electrocardiography, including the PR interval, the QRS duration, and the corrected QT (QTc) space.

Milnacipran has also been reported to improve sexual function and enjoyment in depressed patients (Baldwin, Moreno, & Briley, 2008).

Venlafaxine

Among the 2897 venlafaxine patients in Phase 2 and Phase 3 depression studies reviewed by Rudolph and Derivan (Rudolph & Derivan, 1996) 18% discontinued treatment due to an AE. The more common events (occurring in ≥10% of the venlafaxine-treated patients and at a rate twice that reported among placebo-treated patients) were nausea, insomnia, dizziness, somnolence, constipation, and sweating. By contrast, 6% of 609 patients treated with placebo during clinical trials withdrew because of AEs (Rudolph et al., 1996).

Treatment with venlafaxine is associated with sustained increases in BP in some patients. In placebo-controlled studies with venlafaxine, clinically significant increases in BP (increase in diastolic BP ≥15 mmHg and ≥105 mmHg from baseline) were observed in 5.5% of patients at doses above 200 mg daily (Feighner, 1995). The mean increase in BP was 2.93 mmHg (systolic) and 3.56 mmHg (diastolic) after 8 to 12 weeks of treatment with doses of >75 mg/day (Wyeth Pharmaceuticals, Inc, 2012).

The mean change from baseline in QTc for venlafaxine-treated patients was greater than that for placebo-treated patients (increase of 4.7 milliseconds [ms] for venlafaxine and decrease of 1.9 ms for placebo). The mean change from baseline in HR for venlafaxine-treated patients was significantly higher than that for placebo (a mean increase of 4 bpm for venlafaxine and 1 bpm for placebo). In a flexible-dose study, with venlafaxine doses ranging from 200 to 375 mg/day and mean dose >300 mg/day, venlafaxine-treated patients had a mean increase in HR of 8.5 bpm compared with 1.7 bpm in the placebo group. In addition, a loss of ≥5% or more of body weight occurred in 7% of patients treated with venlafaxine compared to 2% of patients treated with placebo (Wyeth Pharmaceuticals, Inc, 2012). Finally, sexual dysfunction has been noted in patients treated with venlafaxine (Lee et al., 2010; Schweitzer, Maguire, & Ng, 2009).

Abrupt discontinuation has been found to be associated with the appearance of a variety of new symptoms (Wyeth Pharmaceuticals, Inc, 2012).

Duloxetine

Safety data for duloxetine have been pooled from the acute phases of 8 double-blind, placebo-controlled, randomized clinical trials (Hudson et al., 2005). The rates of serious adverse events (SAEs) for duloxetine- and placebo-treated patients were .3% and .6%, respectively ($p = .282$). AEs lead to discontinuation in 9.7% of duloxetine-treated patients, compared to 4.2% of patients receiving placebo ($p < .001$). TEAEs present in duloxetine-treated patients with an incidence ≥5% that were significantly greater than in patients receiving placebo, were nausea, dry mouth, constipation, insomnia, dizziness, fatigue, somnolence, increased sweating, and decreased appetite. Mean changes in BP and HR were small, and the incidence of increases above normal ranges was low. Duloxetine-treated patients had a mean decrease in weight of .5 kg, compared with an increase of .2 kg for patients receiving placebo ($p < .001$).

Thase et al. (2005) further evaluated the effects of duloxetine on cardiovascular safety based on data from the 8 placebo-controlled trials plus active comparator-controlled depression trials. There was a significant increase for duloxetine compared with placebo for HR (1.6 versus −.6 bpm) and for systolic BP (1.0 versus −1.2 mmHg); the difference for diastolic BP (1.1 versus .3) was not significant. Also, the effect of duloxetine on mean changes in supine systolic and diastolic BP was not significantly different from that of fluoxetine or paroxetine. Drug-placebo differences in mean changes in electrocardiograms (eg, QTc, PR, and QRS intervals) were neither statistically nor clinically significant, with the exception of duloxetine 120 mg/day, which significantly decreased PR and QRS intervals compared with placebo.

Delgado et al. (2005) found the incidence of acute treatment-emergent sexual dysfunction is higher with duloxetine compared with placebo, but is significantly lower when compared with paroxetine. However, Dueñas et al. (2011) found treatment-emergent sexual dysfunction in duloxetine and SSRI monotherapy to be comparable (23.4% versus 28.7%, respectively; $p = .087$).

Duloxetine treatment is also associated with discontinuation symptoms. In a pooled analysis of 6 short-term treatment trials in which treatment was stopped abruptly, discontinuation-emergent adverse events (DEAEs) were reported by 44.3% and 22.9% of duloxetine-treated and placebo-treated patients, respectively ($p < .05$). Among duloxetine-treated patients reporting at least 1 DEAE, the mean number of symptoms was 2.4. The DEAEs reported significantly more frequently upon abrupt discontinuation of duloxetine (compared with placebo) were dizziness (12.4%), nausea (5.9%), headache (5.3%), paresthesia (2.9%), vomiting (2.4%), irritability (2.4%), and nightmares (2.0%) (Perahia, Kajdasz, Desaiah, & Haddad, 2005).

Genetic factors may also contribute to individual variations in adverse reactions to SNRIs. For example, findings from duloxetine clinical trials suggest that the incidence of nausea may be higher in patients from East Asia (37%; 60 mg once daily [QD] compared with Caucasian patients [14.4%, pooled analysis; 23.4%, pooled analysis; 29.7%, 60 mg QD]) (Lee et al., 2012).

Summary and Conclusions

Remission in major depression is really the goal of treatment: alleviate a maximum number of depressive symptoms, return to functional normality, and minimize relapse. One of the difficult aspects of depression is its multifaceted nature, with many potential associated symptoms. Pain is an important symptom associated with depression because of its negative impact on patient functionality and the probability of reaching remission.

Research suggests that chronic pain and depression not only co-occur but promote the development of each other, such that chronic pain is a strong predictor of subsequently developing major depression, and vice versa. It has also been suggested that pain and depression co-exist symptomatically because they

are driven by largely overlapping pathophysiological processes in the brain and body (Maletic & Raison, 2009). Antidepressants with a dual (5-HT/NE reuptake inhibition) mechanism of action may be more efficacious in treatment of the PPS associated with depression (Trivedi, 2004). The biological basis for this hypothesis lies in the apparently reciprocal relationship between the descending serotonergic and noradrenergic projections from the brainstem. Dysfunction in these spinal pain modulatory pathways, owing to dysregulation of 5-HT and NE neurotransmission, also believed to play a role in depression, may lead to a hyperalgesic state in patients with depression (Stahl, 2002).

Although all SNRIs have the same mechanism of action, they each also have some unique pharmacologic aspects. Pharmacodynamics and pharmacokinetics of each of the SNRIs may help explain the efficacy patterns, posology, and some AEs of each. Also, to understand the potential for drug interactions and whether dose adjustments are appropriate for a specific patient (including hepatic and renal insufficiency), it is important to consider the intrinsic and extrinsic factors that influence the pharmacokinetics or pharmacodynamics of SNRIs.

Milnacipran has a relatively high potency for NE reuptake inhibition than 5-HT compared to other SNRIs. It is generally given twice daily in MDD treatment due to its short plasma half-life. It has been shown to be superior to placebo in treating depression. However, comparisons with SSRIs have yielded mixed results. Unfortunately, there is little evidence to conclude whether milnacipran is effective in treating PPS associated with depression. The AEs for milnacipran (eg, sweating, urinary hesitancy) tend to be related to NE. Regarding cardiac/BP changes, milnacipran treatment is associated with orthostatic hypotension, but has no apparent effect on electrocardiography.

Venlafaxine has differing degrees of inhibition of NE reuptake depending on dose, whereas 5-HT reuptake inhibition is moderately potent and present at almost at all doses. It has been shown to have somewhat better efficacy than the SSRIs in the treatment of depression. In addition, there is some evidence that venlafaxine reduces PPS associated with depression. However, the dose-response effect related to venlafaxine's ability to block reuptake of NE requires titration up to higher doses in clinical practice. Also, venlafaxine has reduced efficacy and/or reduced tolerability in patients who are poor cytochrome P450 2D6 metabolizers. TEAEs for venlafaxine tend to be more 5-HT-related. However, venlafaxine treatment is associated with NE-related increases in BP, HR, and QTc.

Duloxetine is relatively balanced in its potency of 5-HT and NE reuptake inhibition. It may be administered once daily in MDD treatment. In addition to alleviating the core symptoms of depression, duloxetine may have particular efficacy for PPS associated with depression. There is also some evidence that the efficacy of duloxetine is superior to that of the SSRIs, at least among those patients with more severe symptoms. Duloxetine is the first SNRI approved for treatment of diabetic peripheral neuropathic pain in most countries. It is also approved for fibromyalgia and chronic musculoskeletal pain (i.e., chronic low back pain, osteoarthritis). Duloxetine treatment is associated with a small increase in HR and systolic BP, but not diastolic BP. No electrocardiographic changes have been noted at normal doses.

Direct comparison of the benefits and risks of individual SNRIs can be difficult from the clinical point of view since there are few head to head studies between SNRIs. More comparative clinical and preclinical studies may be of benefit.

In conclusion, although all SNRIs have a similar mechanism of action for MDD treatment, they have different pharma-cologic profiles that may impact clinical outcomes. Careful consideration of the pharmacologic differentiations of SNRIs can help to achieve better efficacy and safety results in the clinical practice of MDD treatment.

Acknowledgements

We thank Dr. Rodney Moore (inVentiv Health Clinical, funded by Eli Lilly and Company) for his assistance in drafting the manuscript.

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