Introduction

Michael E. Thase, MD

ABSTRACT

Major depressive disorder (MDD) is one of the leading causes of disability worldwide and, although many treatment options are available, the percentage of patients brought to remission remains low. Newer antidepressants, including serotonin norepinephrine reuptake inhibitors (SNRIs), have been developed to address this unmet need. Extrapolating from studies of older “dual reuptake inhibitors” such as the tricyclic antidepressant (TCA) clomipramine, it was hoped that therapy with SNRIs would result in high rates of response and remission and relieve a broad array of associated symptoms, yet have a more favorable safety profile than the TCAs. The SNRI class now includes four medications: venlafaxine, duloxetine, milnacipran, and desvenlafaxine. Among these medications, milnacipran is not United States Food and Drug Administration-approved for the treatment of MDD and desvenlafaxine, which is the succinate salt of O-desmethylvenlafaxine (ie, ODV, the principal active metabolite of venlafaxine), was introduced in early 2008. All four SNRIs have established efficacy in MDD, and several members of the class also have been shown to reduce symptoms commonly associated with MDD, including anxiety and pain. When the first SNRI, venlafaxine, was introduced in 1994, it was widely considered a second-line treatment option (ie, used after selective serotonin reuptake inhibitor failure); this ranking was mainly based on dosing and tolerability issues. Introduction of the extended-release formulation of venlafaxine and duloxetine (in 1997 and 2004, respectively, in the US) have addressed some, but not all, of these concerns. Although the four drugs are grouped together as a class, there are important differences among the SNRIs in terms of pharmacologic and pharmacokinetic characteristics. Thus, SNRIs are not interchangeable and vary in their safety and tolerability profiles and, in all likelihood, utility for particular patients.

FOCUS POINTS

• Contemporary pathophysiologic models of major depressive disorder (MDD) include a range of neurotransmitters, neuropeptides, and neuromodulators; however, all of the major drug classes currently used to treat MDD modulate the activity of serotonin (5-HT), norepinephrine (NE), or both.
• Serotonin norepinephrine reuptake inhibitors (SNRIs) were developed to inhibit the uptake of both 5-HT and NE, with the goal of improving efficacy over selective serotonin reuptake inhibitors without significant affinity for other receptors that contribute to safety and tolerability concerns in the older classes of antidepressants.
• All four medications included in the SNRI class (venlafaxine, duloxetine, milnacipran, and desvenlafaxine) have established efficacy in MDD, but there are important pharmacologic and pharmacokinet c differences among the SNRIs likely to be reflected in their efficacy and tolerability profiles.

INTRODUCTION

Major depressive disorder (MDD) is one of the leading causes of disability worldwide, and although many treatment options are available for MDD, the percentage of patients brought to remission remains low.1

The monoamine neurotransmitters serotonin (5-HT) and norepinephrine (NE) have long been believed to play a critical role in both the pathophysiology of MDD and the mechanisms of action of antidepressant drugs.2,3 Although contemporary pathophysiologic models of MDD have expanded to include the roles of other neurotransmitters, neuropeptides, and neuromodulators,4,5 it remains true that all of the major drug classes used to treat MDD modulate the activity of either one or both of these monoamines.6 Between-and-within-class differences in the interactions between antidepressant drugs and the 5-HT and NE systems are likely to contribute to differences in their safety and tolerability profiles as well as their spectrum of efficacy.

Both of the first two classes of antidepressant drugs, monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), acutely increase the availability of 5-HT and NE,
Although selectivity conveyed important advantages for SSRIs versus TCAs, some evidence also suggested one potential drawback: lower efficacy for the most severe depressions. Specifically, two randomized, controlled trials conducted by the Danish University Antidepressant Group in hospitalized patients found that the tertiary amine TCA clomipramine was significantly more effective than the SSRIs citalopram and paroxetine in severe MDD. Subsequent meta-analyses that included these and other inpatient studies documented greater efficacy for TCAs compared with SSRIs. As this advantage was almost entirely accounted for by a subset of studies utilizing the tertiary amine TCAs, particularly by the studies of clomipramine, the most credible explanation was that antidepressants that modulate both 5-HT and NE neurotransmission have a broader spectrum of efficacy for severe MDD. That meta-analysis also documented comparable efficacy among the secondary amine TCAs, which primarily inhibit NE uptake, and the SSRIs, which suggested that the two pathways had comparable antidepressant activity for severely depressed patients. These observations were further supported by the results of an influential study that found that patients treated with the combination of fluoxetine and desipramine had superior outcomes compared with those of a historical control group treated with desipramine alone.

**SNRI DEVELOPMENT AND USE**

The term “serotonin norepinephrine reuptake inhibitor” (SNRI) was coined to describe a new class of compounds synthesized to inhibit uptake of 5-HT and NE, without significant affinity for other receptors. SNRIs were developed with the hope of approximating the efficacy profile of a tertiary amine TCA and the safety profile of an SSRI. The SNRI class now includes four compounds: venlafaxine, duloxetine, milnacipran (United States Food and Drug Administration-approved for the treatment of fibromyalgia only), and desvenlafaxine (US launch: early 2008). Following SSRIs, SNRIs are the most widely used class of antidepressants in the US.

**Venlafaxine**

The first SNRI, venlafaxine, was introduced in the US in 1994 and was considered by most practitioners to be a second-line treatment option for several reasons, including dosing requirements and safety and tolerability issues. The original, immediate-release (IR) formulation of venlafaxine had a recommended starting dose of 75 mg/day, administered in two or three divided doses. When used primarily following SSRI nonresponse, upward titration was often necessary and efficacy was established for doses up to 375 mg/day. Venlafaxine inhibits the NE transporter weakly in vitro but NE transporter antagonism in vivo has been demonstrated to be dose dependent. It is
widely believed that venlafaxine may function as an SSRI at low dose (eg, 75 mg/day) and as an SNRI at higher doses (eg, 225–375 mg/day),37 with efficacy for different patient populations at different doses, and side effects related to increasing NE emerging with increasing dose. Venlafaxine IR was better tolerated than TCAs such as amitriptyline and imipramine but not as well tolerated as SSRIs, with somewhat higher rates of nausea early in the course of therapy and higher rates of other side effects that reflect the compound’s noradrenergic activity (ie, constipation, dry mouth, dizziness, and blurred vision).30,38,39 Like TCAs and SSRIs, venlafaxine has been associated with sexual dysfunction.48 Incidence of spontaneously reported sexual dysfunction (abnormal ejaculation/aversion/gain) is listed as 12% of venlafaxine IR-treated patients in the prescribing information32; studies that specifically assessed sexual functioning found rates of sexual dysfunction of up to 67%, similar to rates reported for several of the SSRIs (62% to 73%).40,41 Another important clinical characteristic of venlafaxine IR was the relatively high incidence of discontinuation symptoms following abrupt cessation of therapy. Zajecka and colleagues42 found reports of discontinuation symptoms for venlafaxine IR (half-life: 5 hrs) to be generally comparable to those for short half-life SSRIs (paroxetine: 21 hrs; fluvoxamine: 16 hrs).43,44 Venlafaxine IR therapy was also associated with a dose-dependent risk of elevated blood pressure, ranging from 2% of patients receiving <100 mg/day venlafaxine (ie, the same percentage as placebo) to 9% of patients receiving >300 mg/day.45

In 1997, an extended-release (ER) formulation of venlafaxine was introduced, which permitted once-daily dosing. Venlafaxine ER has a lower peak plasma concentration and a longer period of duration to reach peak compared with equivalent doses of the IR formulation.46 Improved tolerability with the ER formulation was suggested by results of one head-to-head trial versus the IR formulation47,48 and this, coupled with the simpler recommended dosing schedule and emerging evidence of possible superiority in head-to-head comparative studies versus several members of the SSRI class (eg, venlafaxine remission rate: 45%, SSRI: 35% in a pooled analysis of data from eight clinical trials; response rates varied across individual trials),49-53 contributed to greater acceptance of this SNRI as a potential first-line therapy for MDD.54,55

As reviewed elsewhere in this supplement in more detail,56 it is important to understand that results of individual studies in a meta-analyses can be influenced by factors such as the patient population, study medication doses, and duration of therapy. Subsequent meta-analyses of larger data sets have generally confirmed a modest (ie, 5% to 10%) advantage versus SSRIs as a class and, in particular, in studies comparing venlafaxine with fluoxetine.38,57-59 A broad spectrum of efficacy was underscored by the subsequent FDA approval of venlafaxine ER for treatment of generalized anxiety disorder, social anxiety disorder, and panic disorder.60 Early studies indicated that venlafaxine IR may have particular utility for treatment-resistant depression,61,62 but results from more recent trials have been mixed.63-69

**Duloxetine**

Duloxetine was the second SNRI to receive FDA approval for the treatment of MDD (2004), although milnacipran, which has not received FDA approval for MDD, was available elsewhere in the world several years earlier. Several pharmacologic characteristics distinguish duloxetine from venlafaxine, including higher in vitro potency for inhibition of NE uptake, a higher estimated 5-HT/NE selectivity ratio (1/9 versus 1/30), greater binding to plasma protein, lack of a dose-response relationship, and a lower incidence of treatment-emergent high blood pressure.45,60-72 Nevertheless, similar to venlafaxine, a modest efficacy advantage compared with SSRIs was observed in a meta-analysis of early comparative studies (remission rates of 35.9% versus 28.6%, respectively, for patients with moderate-to-severe MDD).73 Of note, there was no advantage for duloxetine therapy among the subset of patients with milder MDD in this meta-analysis.73 Moreover, the apparent superiority of duloxetine in patients with more severe depressive symptoms must be qualified by the caveat that these studies compared minimum doses of SSRIs (ie, fluoxetine or paroxetine at 20 mg/day) against doses of duloxetine that are higher than currently recommended (ie, 80–120 mg/day). In addition to MDD, duloxetine is FDA-approved for treatment of generalized anxiety disorder and for pain management in patients with diabetic peripheral neuropathy.71

**Milnacipran**

Milnacipran differs from both venlafaxine and duloxetine in terms of lower in vitro potency for inhibition of 5-HT, distinguishing it as a relatively more noradrenergic drug within the SNRI class, with a 5-HT/NE selectivity ratio of ~1/2.70,74 In contrast to venlafaxine and duloxetine, a meta-analysis of comparative studies suggested no efficacy advantage versus SSRIs.75

**Desvenlafaxine**

The latest addition to the SNRI class is desvenlafaxine (administered as desvenlafaxine succinate), which is a formulation of O-desmethylvenlafaxine (ODV), the principal active metabolite of venlafaxine.76 Desvenlafaxine was FDA-approved for the treatment of MDD in 2008.27 Unlike the parent compound, which is metabolized to ODV in the liver by cytochrome P450 (CYP) 2D6,48 desvenlafaxine has no active metabolite, and its elimination is not altered by genetic alterations in CYP 2D6 activity.27,56 When compared with the parent compound, desvenlafaxine has greater in vitro potency for inhibition of NE uptake (5-HT/NE selectivity ratio: 1/14) and greater bioavailability, with a lower recommended therapeutic dose (50 mg/day) and no evidence of a dose-therapeutic response relationship in placebo-controlled studies.27,60,70,77,78
CONCLUSION

The goal of this supplement is to provide a comprehensive review of the SNRI class of medications. This supplement includes three articles that discuss characteristics of the class as a whole and examine differences among the four compounds, focusing on their role in the treatment of MDD and associated pain and anxiety symptoms.

Pedro L. Delgado, MD, reviews the neuropharmacology of SNRIs. After an overview of the dual action hypothesis, Dr. Delgado explores both the central and peripheral effects of SNRIs and their interactions with 5-HT and NE systems. He also discusses the emerging understanding of the impact of genetic polymorphisms on therapeutic response and tolerability, and implications for prescribing and managing SNRIs in patient populations.

George I. Papakostas, MD, reviews evidence for efficacy of the class for treating MDD and examines study results supporting efficacy of SNRIs in different clinical settings and patient populations. Dr. Papakostas also provides an overview of the clinical trial data for SNRI treatment of anxiety and pain, both of which occur at high rates with MDD.

Finally, Richard C. Shelton, MD, compares the individual members of the SNRI class. Within the class, the four compounds vary in their affinities for the 5-HT and NE transporters and their pharmacokinetic profiles.

These differences are likely to be reflected in their efficacy and tolerability. Dr. Shelton highlights the differences in symptom relief of the four SNRIs as well as differences in their safety and tolerability. He also discusses unmet needs with existing SNRIs and other available antidepressants and future research directions that may yield continued improvement in the treatment of MDD.

REFERENCES


