Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

Summary

- Serotonin norepinephrine reuptake inhibitors (SNRIs) differ from selective serotonin reuptake inhibitors (SSRIs) in that they also inhibit the reuptake of norepinephrine, as the class name indicates, but their potency with regard to serotonin reuptake inhibition is comparable to that of the SSRIs.
- SNRIs are used for the treatment of numerous psychiatric disorders, including major depression and anxiety disorders.[49961][58403][58404][50550][50542]
- Despite the expectation that dual receptor activity might provide greater clinical efficacy, SNRIs as a class appear to provide similar response rates to SSRIs in the treatment of major depression in adults.[50533][50534]
- Determinants of which SNRI to choose include indication, drug interactions, drug-specific precautions (e.g., renal disease, hepatic disease), and response history of the patient.
- Drug interactions may occur with duloxetine, desvenlafaxine, and venlafaxine due to metabolism by CYP isoenzymes. Milnacipran and levomilnacipran have minimal CYP450 metabolism, and clinically relevant interactions related to CYP metabolism are not expected.
- Duloxetine should not be used in patients with hepatic impairment or risk factors for hepatic impairment (e.g., alcoholism). Milnacipran, levomilnacipran, venlafaxine, and desvenlafaxine can be used in patients with hepatic impairment; however, dosage adjustments for venlafaxine and desvenlafaxine are required.
- Drug-specific dosage adjustments are required for desvenlafaxine, duloxetine, levomilnacipran, milnacipran, and venlafaxine in the presence of renal dysfunction and are based upon the severity of the renal impairment.
- Milnacipran is the only SNRI not approved in the U.S. for the treatment of major depressive disorder (MDD), but the drug is effective for MDD and is approved in some other countries for this indication.[50546]
- Like tricyclic antidepressants (TCAs), the noradrenergic effects of the SNRIs may explain the effectiveness of some of these agents in the treatment of various pain syndromes. For example, milnacipran and duloxetine are used for fibromyalgia, and duloxetine is effective for diabetic neuropathy.

SNRIs inhibit the reuptake of both serotonin and norepinephrine. Although this reuptake blockade is thought to contribute to the therapeutic effects of SNRIs in depression and anxiety, the exact mechanism is not known. The members of the class differ in their relative potency at serotonin and norepinephrine auto-receptors; duloxetine and desvenlafaxine demonstrate a 10-fold higher selectivity for serotonin reuptake inhibition than norepinephrine reuptake inhibition and venlafaxine has a 30-fold higher affinity for the reuptake inhibition of serotonin compared to norepinephrine. Conversely, levomilnacipran and milnacipran demonstrate a 2-fold and 3-fold greater potency for norepinephrine reuptake inhibition than serotonin reuptake inhibition, respectively. Norepinephrine receptor blockade is considered important in the treatment of pain, as SSRIs have not been proven efficacious for pain disorders. Thus, some SNRIs, including milnacipran and duloxetine, have FDA-approved indications in the treatment of some pain disorders. All SNRIs inhibit serotonin uptake in human platelets, which has been associated with an increased risk of bleeding adverse events. SNRIs do not have a significant affinity for histaminergic, muscarinic, alpha1-adrenergic, postsynaptic serotonin or dopamine, GABA, or glutamate receptors in vitro, nor do they inhibit monoamine oxidase (MAO). Duloxetine and venlafaxine at high doses weakly inhibit the reuptake of dopamine, which may contribute to effects on blood pressure.[44281][50533][50534][50535][50536][50537][50540][64700]

Comparative Efficacy

Meta-Analysis of SNRIs vs. SSRIs for Depression[50533]

	Venlafaxine vs Fluoxetine	Duloxetine vs Escitalopram	Milnacipran vs Fluoxetine
SNRI, Responders[a] (n)/total treated[b] (N) (%)	679/1116 (61)	260/562 (46)	156/336 (46)
SSRI, responders[a] (n)/total treated[b] (N) (%)	607/1126 (54)	286/558 (51)	106/224 (47)
Odds ratio SNRI to SSRI (95% CI)	1.36 (1.14-1.62)[c]	0.77 (0.52-1.13)	0.87 (0.54-1.39)
Efficacy conclusion	Venlafaxine had a significantly higher response rate than fluoxetine	No significant difference in efficacy between duloxetine and escitalopram	No significant difference in efficacy between milnacipran and fluoxetine
SNRI, All-cause withdrawal (n)/total randomized[d] (N) (%)	302/1220 (25)	131/411 (32)	138/336 (41)
SSRI, all-cause withdrawal (n)/total randomized[d] (N) (%)	290/1226 (24)	87/414 (21)	83/224 (37)
Odds ratio SNRI to SSRI (95% CI)	1.07 (0.88-1.29)	1.93 (0.99-3.77)	1.02 (0.71-1.46)
Acceptability conclusion	No significant difference in acceptability between venlafaxine and fluoxetine	No significant difference in acceptability between duloxetine and escitalopram	No significant difference in acceptability between milnacipran and fluoxetine

[a]Response = a reduction of at least 50% from the baseline score on the Hamilton Depression Rating Scale (HAM-D) or Montgomery-Asberg depression rating scale (MADRS), or a score of "much improved" or "very much improved" on the Clinical Global Impression scale (CGI) at 8 weeks (intention to treat; last observation carried forward [ITT-LOCF]); [b]ITT population; [c]statistically significant (lower limit of 95% confidence interval [CI] 1 or greater); [d]safety population

SNRIs Comparative Efficacy Trials

Citation/Study Name	Design/Regimen	Results	Conclusion
Perahia DG, et al. J Psychiatr Res. 2008;42:22-34 [50544]	Data pooled from 2 similarly designed, double-blind, parallel group studies; patients with major depressive disorder were randomized to duloxetine (n=330) or venlafaxine XR (n=337) x 12-weeks The primary outcome measure was Global Benefit-Risk (GBR). In the GBR analysis, benefit was defined as remission at end point (17-item HAM-D score of 7 or less). Risk was defined by 4 categories: i) patients having no adverse events (AEs); ii) AEs with no severity rating greater than moderate; iii) AEs with at least 1 severity rating of severe; and iv) having discontinued with a reason of self-reported AE. GBR scores ranged from +5 (remission and no AEs) to -5 (no remission and discontinued due to AE)	**GBR at 12 weeks (LOCF, linear score, mean [SE]):** duloxetine vs venlafaxine, -0.35 (0.21) vs -0.12 (0.20), p=0.44 **Completion rates:** 74.5% for venlafaxine XR vs 64.8% for duloxetine, p < 0.01 **Remission rates at 12 weeks:** duloxetine, 48.1% vs venlafaxine, 50.3% **Common AEs:** nausea (43.6% vs 35.0%, p=0.02) and dizziness (16.1% vs 10.4%, p=0.03) were more frequent in duloxetine group **Discontinuation due to AEs:** occurred more frequently in the duloxetine group at 12 weeks (14.5% vs 9.2%; p=0.03)	Both drugs had negative GBR scores at 12 weeks, suggesting that this outcome measure may have been too strict. About one-half of patients taking either drug achieved remission at 12 weeks. Venlafaxine was slightly but significantly better tolerated as evidenced by fewer discontinuations due to AEs and higher study completion rates. The study was sponsored by Lilly, the maker of duloxetine

Cunningham LA. Ann Clin Psychiatry. 1997;9:157-164 [50545]	Double-blind, placebo-controlled comparison of the efficacy and safety of venlafaxine XR and venlafaxine immediate-release (IR) x 12 weeks. Primary efficacy variables were the 21-item HAM-D Rating Scale total score and depressed mood item, the MADRS total scores, and the CGI severity scale. Safety/tolerability were assessed by AEs, physical exam, sentinel events, vital signs, electrocardiogram, and lab tests	**Efficacy at week 12: HAM-D:** XR, 9.4; IR, 12.3; placebo, 15.8 ($p < 0.05$ favoring XR vs IR) **MADRS:** XR, 10.6; IR, 13.3; placebo, 18.3 ($p < 0.05$ favoring XR vs IR) **CGI:** XR, 2.08; IR, 2.67; placebo, 3.18 ($p < 0.05$ favoring XR vs IR) Both XR and IR were superior to placebo at weeks 6 and 12 **Completion rates:** XR group had a higher rate (71%) than IR (60%) or placebo (59%) (p=NS) **AEs:** Nausea most common in XR and IR (45% each); sexual dysfunction in men highest in XR (27%) vs IR (6%) and placebo (0%)	Venlafaxine XR exhibited superiority over venlafaxine IR at week 12 for all efficacy variables. The most common AE was nausea, regardless of formulation. The results indicate that venlafaxine XR is safe, effective, and well-tolerated. Sexual dysfunction in men was higher in the XR group
Tourian KA, et al. Clin Ther. 2009;31(Pt 1):1405-1423 [44282]	Double-blind, duloxetine-referenced, placebo-controlled, parallel-group, 8-week study comparing desvenlafaxine (50 or 100 mg/day) to duloxetine (60 mg/day) in 615 adults with major depressive disorder (HAMD-17 score of 20 or more). Primary outcome measure was HAMD-17 total score at final evaluation. Additional measures included the CGI-I, MADRS, and CGI-S. Tolerability assessments included discontinuation rates, AEs, vital signs, and lab tests. Post hoc pooled analysis was performed using data from the current study and 2 previous similar studies that compared the efficacy and tolerability of desvenlafaxine with placebo for major depressive disorder	**HAMD-17:** desvenlafaxine 100 mg/day (-10.5, p=0.03) and duloxetine 60 mg/day (-10.3, $p < 0.05$) groups compared with placebo (-8.7). Desvenlafaxine 50 mg did not differ from placebo. **CGI-I, MADRS, and CGI-S**: desvenlafaxine 100 mg/day and duloxetine 60 mg/day had significantly better scores compared with placebo; desvenlafaxine 50 mg was not superior to placebo. **Discontinuation rates due to AEs**: 5%, 7%, 13%, and 6% for the desvenlafaxine 50 mg/day, desvenlafaxine 100 mg/day, duloxetine 60 mg/day, and placebo groups, respectively. **Post hoc pooled HAM-D(17)** (N=1388): desvenlafaxine 50 mg/day (-11.5, $p < 0.001$), desvenlafaxine 100 mg/day (-11.8, $p < 0.001$) were superior to placebo (-9.6)	The pooled analysis showed that desvenlafaxine 50 mg and 100 mg daily were similarly significantly more efficacious than placebo on the primary outcome measure. In the duloxetine-referenced trial, only the 100 mg dose was superior to placebo and equivalent in efficacy to duloxetine. Both doses of desvenlafaxine had placebo-like tolerability profiles

Sechter D, et al. J Affect Disord. 2004;83(2-3):233-236 [50546]	A 6-week double-blind, randomized, parallel group study compared milnacipran (100 mg/day) with paroxetine (20 mg/day) in 300 outpatients with major depression. Efficacy (ITT-LOCF) was evaluated using HAMD17, MADRS, and CGI. Safety and tolerability were assessed in standard fashion	**HAMD17, MADRS, and CGI:** No significant differences were noted on any outcome measure between groups **Safety/tolerability:** No major safety issues were noted; tolerability was similar	Both milnacipran and paroxetine were effective and well-tolerated by outpatients with major depression treated for 6 weeks. After treatment discontinuation milnacipran was associated with fewer emergent symptoms

Drug Interactions

MAO inhibitors

SNRIs are contraindicated in patients receiving MAO inhibitors (MAOIs) or within 2 weeks of their discontinuation due to the risk of serotonin syndrome. Medications with MAOI activity, such as linezolid or intravenous methylene blue, are also contraindicated for use with SNRIs because of an increased risk of serotonin syndrome.[23430][23431][28275][29934][33715][34940][55469]

SSRIs, SNRIs and other serotonergic drugs

Any use of an SNRI with other serotonergic agents increases the likelihood of serotonergic adverse effects and should be monitored closely. Drugs that have serotonergic properties include opiates, triptans, most antidepressants, amphetamines, St. John's wort, tramadol, lithium, buspirone, and others. [23430][23431][28275][29934][33715][34940][55469]

Antithrombotic drugs

Anticoagulants, antiplatelet drugs (e.g., aspirin), and nonsteroidal anti-inflammatory drugs (NSAIDs) should be administered with caution to any patient taking an SNRI. Platelet aggregation may be impaired by SNRIs due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication. Patients should be instructed to monitor for signs and symptoms of bleeding while taking an SNRI with an anticoagulant medication and to promptly report any bleeding events to the practitioner. [23430][23431][28275][29934][33715][34940][55469]

Drugs that inhibit CYP2D6 or CYP1A2

Levomilnacipran and milnacipran are not metabolized to any significant extent by CYP450 isoenzymes and are not inducers or inhibitors of any of these isoenzymes. Venlafaxine is metabolized by CYP2D6, and CYP2D6 inhibitors may increase venlafaxine concentrations. A dose-related CYP2D6 inhibitory effect has been observed with desvenlafaxine; therefore, the dose of primary CYP2D6 substrates should be reduced by up to one-half if coadministered with desvenlafaxine 400 mg/day. Duloxetine is metabolized by CYP1A2 and CYP2D6; inhibitors of CYP1A2 and CYP2D6 may increase duloxetine concentrations.[23430][23431][28275][29934][33715][34940][55469]

Appendix A

Therapeutic Use Table

Indications	Desvenlafaxine	Desvenlafaxine Succinate	Duloxetine	Levomilnacipran	Milnacipran HCl	Venlafaxine Hydrochloride
Renal Impairment Dosing Adjustment	Yes	Yes	Yes	Yes	Yes	Yes
Hepatic Impairment Dosing Adjustment	Yes	Yes	Yes			Yes
depression	Yes	Yes	Yes	Yes	Yes †	Yes
diabetic neuropathy			Yes			Yes †
fibromyalgia			Yes		Yes	Yes †
generalized anxiety disorder (GAD)			Yes			Yes
hot flashes	Yes †	Yes †				Yes †
menopause	Yes †	Yes †				Yes †
musculoskeletal pain			Yes			
osteoarthritis			Yes			
panic disorder						Yes
premenstrual dysphoric disorder (PMDD)						Yes †
social phobia (social anxiety disorder)						Yes
urinary incontinence			Yes †			

Yes – Labeled
Yes † – Off-label

Appendix B

Top 20 Adverse Reactions / Side Effects Table

Adverse Reaction / Side Effect	Desvenlafaxine	Desvenlafaxine Succinate	Duloxetine	Levomilnacipran	Milnacipran HCl	Venlafaxine Hydrochloride
anorexia	5 - 10%	5 - 10%	7 - 10%	3%	Reported	8 - 18%
constipation	9 - 14%	9 - 14%	9 - 11%	9%	15 - 16%	8 - 15%
dizziness	10 - 16%	10 - 16%	8 - 10%	Reported	10 - 11%	11 - 20%
ejaculation dysfunction	<7%	<7%	2 - 3%	5%	>2%	8 - 19%
hyperhidrosis	10 - 21%	10 - 21%	<6%	9%	8 - 9%	6.7 - 19.3%
hypertension	0.7 - 2.3%	0.7 - 2.3%	Reported	3%	4 - 7%	0.5 - 13%
impotence (erectile dysfunction)	3 - 11%	3 - 11%	4%	6%	>2%	4 - 5%
nausea	22 - 41%	22 - 41%	4 - 24%	17%	35 - 39%	21 - 58%
withdrawal	22 - 27%	22 - 27%	>1%	Reported	Reported	0.1 - 1%
drowsiness	4 - 12%	4 - 12%	9 - 12%		>1%	12 - 23%
insomnia	9 - 15%	9 - 15%	7 - 11%		12%	18 - 23%
orthostatic hypotension	<8%	<8%	0.1 - 1%	11.6%		0.1 - 1%
weight loss	Reported	Reported	0.1 - 14%		>1%	4 - 47%
xerostomia	11 - 25%	11 - 25%	2 - 14%		5%	12 - 22%
asthenia	<2%	<2%	10 - 11%			8 - 15%
fatigue	7 - 11%	7 - 11%	7 - 11%		>1%	
abdominal pain			5 - 13%	<2%	3%	
headache			13 - 18%		17 - 19%	25 - 38%
hot flashes			0.1 - 1%	3%	11 - 12%	
weakness						8 - 19%

Appendix C

Safety Issues Table

Safety Issue	Desvenlafaxine	Desvenlafaxine Succinate	Duloxetine	Levomilnacipran	Milnacipran HCl	Venlafaxine Hydrochloride
REMS						
MedGuide	Yes	Yes	Yes	Yes	Yes	Yes
children	BBW	BBW	BBW	BBW	BBW	BBW
desvenlafaxine hypersensitivity	X	X				
MAOI therapy	X	X	X	X	X	X
milnacipran hypersensitivity				X		
suicidal ideation	BBW	BBW	BBW	BBW	BBW	BBW
venlafaxine hypersensitivity	X	X				X

X – Contraindicated
X-BBW – Contraindicated and Black Box Warning
BBW – Black Box Warning, Not Contraindicated
Yes – REMS or MedGuide is available