# 27 - 29.27 Selective SerotoninNorepinephrine Reupt

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Assoc Nurses AIDS Care. 2013;24(1 Suppl):S135–S145. Tuncel A, Nalcacioglu V, Ener K, Aslan Y, Aydin O, Atan A. Sildenafil citrate and tamsulosin combination is not superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction. World J Urol. 2010;28(1):17–22. 29.27 Selective Serotonin–Norepinephrine Reuptake Inhibitors There are currently four serotonin–norepinephrine reuptake inhibitors (SNRIs) approved for use in the United States: venlafaxine (Effexor and Effexor XR), desvenlafaxine succinate (DVS; Pristiq), duloxetine (Cymbalta), and levomilnacipran (Fetzima). A fifth SNRI, milnacipran (Savella), available in other countries as an antidepressant, has U.S. Food and Drug Administration (FDA) approval in the United States as a treatment for fibromyalgia. The term SNRI reflects the belief that the therapeutic effects of these medications are mediated by concomitant blockade of neuronal serotonin (5-HT) and norepinephrine uptake transporters. The SNRIs are also sometimes referred to as dual reuptake inhibitors, a broader functional class of antidepressant medications that includes tricyclic antidepressants (TCAs) such as clomipramine (Anafranil) and, to a lesser extent, imipramine (Tofranil) and amitriptyline (Elavil). What distinguishes the SNRIs from TCAs is their relative lack of affinity for other receptors, especially muscarinic, histaminergic, and the families of α- and β-adrenergic receptors. This distinction is an important one because the SNRIs have a more favorable tolerability profile than the older dual reuptake inhibitors. VENLAFAXINE AND DESVENLAFAXINE Therapeutic Indications Venlafaxine is approved for treatment of four disorders: major depressive disorder, generalized anxiety disorder, social anxiety disorder, and panic disorder. Major depressive disorder is currently the only FDA-approved indication for DVS. Depression. The FDA does not recognize any class of antidepressant as being more effective than any other. This does not mean

that differences do not exist, but no study to date has sufficiently demonstrated such superiority. It has been argued that direct modulation of serotonin and norepinephrine may convey greater antidepressant effects than are exerted by medications that selectively enhance only noradrenergic or serotoninergic neurotransmission. This greater therapeutic benefit could result from an acceleration of postsynaptic adaptation to increased neuronal signaling; simultaneous activation of two pathways for intracellular signal transduction; additive effects on the activity of relevant genes such as brain-derived neurotrophic factor; or, quite simply, broader coverage of depressive symptoms. Clinical evidence supporting this hypothesis first emerged in a pair of studies conducted by the Danish University Antidepressant Group, which found an advantage for the dual reuptake inhibitor clomipramine

compared with the selective serotonin reuptake inhibitors (SSRIs) citalopram (Celexa) and paroxetine (Paxil). Another report, which compared the results of a group of patients prospectively treated with the combination of the TCAs desipramine (Norpramin) and fluoxetine (Prozac) with a historical comparison group treated with desipramine alone, provided additional support. A meta-analysis of 25 inpatient studies comparing the efficacy of TCAs and SSRIs yielded the strongest evidence. Specifically, although the TCAs were found to have a modest overall advantage, superiority versus SSRIs was almost entirely explained by the studies that used the TCAs that are considered to be dual reuptake inhibitors—clomipramine, amitriptyline, and imipramine. Meta-analyses of head-to-head studies suggest that venlafaxine has the potential to induce higher rates of remission in depressed patients than do the SSRIs. This difference of the venlafaxine advantage is about 6 percent. DVS has not been extensively compared with other classes of antidepressants with respect to efficacy. Generalized Anxiety Disorder. The extended-release formulation of venlafaxine is approved for treatment of generalized anxiety disorder. In clinical trials lasting 6 months, dosages of 75 to 225 mg a day were effective in treating insomnia, poor concentration, restlessness, irritability, and excessive muscle tension related to generalized anxiety disorder. Social Anxiety Disorder. The extended-release formulation of venlafaxine is approved for treatment of social anxiety disorder. Its efficacy was established in 12week studies. Other Indications. Case reports and uncontrolled studies have indicated that venlafaxine may be beneficial in the treatment of obsessive-compulsive disorder, panic disorder, agoraphobia, social phobia, attention-deficit/hyperactivity disorder, and patients with a dual diagnosis of depression and cocaine dependence. It has also been used in chronic pain syndromes with good effect. Precautions and Adverse Reactions Venlafaxine has a safety and tolerability profile similar to that of the more widely prescribed SSRI class. Nausea is the most frequently reported treatment-emergent adverse effect associated with venlafaxine and DVS therapy. Initiating therapy at lower dosages may also attenuate nausea. When extremely problematic, treatment-induced nausea can be controlled by prescribing a selective 5-HT3 antagonist or mirtazapine (Remeron). Venlafaxine and DVS therapy is associated with sexual side effects, predominantly decreased libido and a delay to orgasm or ejaculation. The incidence of these side effects may exceed 30 to 40 percent when there is direct, detailed assessment of sexual function. Other common side effects include headache, insomnia, somnolence, dry mouth,

dizziness, constipation, asthenia, sweating, and nervousness. Although several side effects are suggestive of anticholinergic effects, these drugs have no affinity for muscarinic or nicotinic receptors. Thus, noradrenergic agonism is likely to be the culprit. Higher-dose venlafaxine therapy is associated with an increased risk of sustained elevations of blood pressure (BP). Experience with

the instant-release (IR) formulation in studies of depressed patients indicated that sustained hypertension was dose related, increasing from 3 to 7 percent at doses of 100 to 300 mg per day and to 13 percent at doses greater than 300 mg per day. In this dataset, venlafaxine therapy did not adversely affect BP control of patients taking antihypertensives and actually lowered mean values of patients with elevated BP readings before therapy. In controlled studies of the extended-release formulation, venlafaxine therapy resulted in only approximately 1 percent greater risk of high BP when compared with placebo. Arbitrarily capping the upper dose of venlafaxine used in these studies thus greatly attenuated concerns about elevated BP. When higher doses of the extended-release formulation are used, however, monitoring of BP is recommended. Venlafaxine and DVS are commonly associated with a discontinuation syndrome. This syndrome is characterized by the appearance of a constellation of adverse effects during a rapid taper or abrupt cessation, including dizziness, dry mouth, insomnia, nausea, nervousness, sweating, anorexia, diarrhea, somnolence, and sensory disturbances. It is recommended that, whenever possible, a slow taper schedule should be used when longer-term treatment must be stopped. On occasion, substituting a few doses of the sustained-release formulation of fluoxetine may help to bridge this transition. There were no overdose fatalities in premarketing trials of venlafaxine, although electrocardiographic changes (e.g., prolongation of QT interval, bundle branch block, QRS interval prolongation), tachycardia, bradycardia, hypotension, hypertension, coma, serotonin syndrome, and seizures were reported. Fatal overdoses have been documented subsequently, typically involving venlafaxine ingestion in combination with other drugs, alcohol, or both. Information concerning use of venlafaxine and DVS by pregnant and nursing women is not available at this time. Venlafaxine and DVS are excreted in breast milk. Clinicians should carefully weigh the risks and benefits of venlafaxine use by pregnant and nursing women. Drug Interactions Venlafaxine is metabolized in the liver primarily by the CYP2D6 isoenzyme. Because the parent drug and principal metabolite are essentially equipotent, medications that inhibit this isoenzyme usually do not adversely affect therapy. Venlafaxine is itself a relatively weak inhibitor of CYP2D6, although it can increase levels of substrates, such as desipramine or risperidone (Risperdal). In vitro and in vivo studies have shown venlafaxine to cause little or no inhibition of CYP1A2, CYP2C9, CYP2C19, and CYP3A4. Venlafaxine is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) because of the risk of a pharmacodynamic interaction (i.e., serotonin

syndrome). An MAOI should not be started for at least 7 days after stopping venlafaxine. Few data are available regarding the combination of venlafaxine with atypical neuroleptics, benzodiazepines, lithium (Eskalith), and anticonvulsants; therefore, clinical judgment should be exercised when combining medications. Laboratory Interferences Data are not currently available on laboratory interferences with venlafaxine. Dosage and Administration Venlafaxine is available in 25-, 37.5-, 50-, 75-, and 100-mg tablets and 37.5-, 75-, and 150-mg extended-release capsules. The tablets and the extended-release capsules are equally potent, and persons stabilized with one can switch to an equivalent dosage of the other. Because the immediate-release tablets are rarely used due to their tendency to cause nausea and the need for multiple daily doses, the dosage recommendations that follow refer to use of the extended-release capsules. In depressed persons, venlafaxine demonstrates a dose–response curve. The initial therapeutic dosage is 75 mg a day given once a day. However, most persons are started at a dosage of 37.5 mg for 4 to 7 days to minimize adverse effects, particularly nausea. A convenient starter kit for the drug contains a 1-week supply of both the 37.5- and 75mg strengths. If a rapid titration is preferred, the dosage can be raised to 150 mg per day after day 4. As a rule, the dosage can be raised in increments of 75

mg a day every 4 or more days. Although the recommended upper dosage of the extended-release preparation (venlafaxine XR) is 225 mg per day, it is approved by the FDA for use at dosages up to 375 mg a day. The dosage of venlafaxine should be halved in persons with significantly diminished hepatic or renal function. If discontinued, venlafaxine use should be gradually tapered over 2 to 4 weeks to avoid withdrawal symptoms. There are minor differences in the doses used for major depression, generalized anxiety disorder, and social anxiety disorder. In the treatment of these disorders, for example, a dose–response effect has not been found. In addition, lower mean dosages are typically used, with most patients taking 75 to 150 mg per day. DVS is available as 50- and 100-mg extended-release tablets. The therapeutic dose for most patients is 50 mg a day. Although some patients may need higher doses, in clinical trials, no greater therapeutic benefit was noted when the dose was increased. At higher doses, adverse event and discontinuation rates were increased. DULOXETINE Pharmacological Actions Duloxetine is formulated as a delayed-release capsule to reduce the risk of severe nausea associated with the drug. It is well absorbed, but there is a 2-hour delay before absorption begins. Peak plasma concentrations occur 6 hours after ingestion. Food

delays the time to achieve maximum concentrations from 6 to 10 hours and reduces the extent of absorption by about 10 percent. Duloxetine has an elimination half-life of about 12 hours (range, 8 to 17 hours). Steady-state plasma concentrations occur after 3 days. Elimination is mainly through the isozymes CYP2D6 and CYP1A2. Duloxetine undergoes extensive hepatic metabolism to numerous metabolites. About 70 percent of the drug appears in the urine as metabolites and about 20 percent is excreted in the feces. Duloxetine is 90 percent protein bound. Therapeutic Indications Depression. In contrast to venlafaxine, a small number of studies have compared duloxetine with the SSRIs. Although these studies are suggestive of some advantage in efficacy, their findings are limited by the use of fixed, low starting doses of paroxetine and fluoxetine, but dosages of duloxetine in some studies were as high as 120 mg per day. Any inferences on whether duloxetine is superior to the SSRIs in any aspect of treatment for depression thus await more evidence from properly designed trials. Neuropathic Pain Associated with Diabetes and Stress Urinary Incontinence. Duloxetine is the first drug to be approved by the FDA as a treatment for neuropathic pain associated with diabetes. The drug has been studied for its effects on physical symptoms, including pain, in depressed patients, but these effects have not been compared with those seen with other widely used agents such as venlafaxine and the TCAs. Duloxetine is currently awaiting approval as a treatment for stress urinary incontinence, the inability to voluntarily control bladder voiding, which is the most frequent type of incontinence in women. The action of duloxetine in the treatment of stress urinary incontinence is associated with its effects in the sacral spinal cord, which in turn increase the activity of the striated urethral sphincter. Duloxetine will be marketed under the name Yentreve for this indication. Precautions and Adverse Reactions. The most common adverse reactions are nausea, dry mouth, dizziness, constipation, fatigue, decreased appetite, anorexia, somnolence, and increased sweating. Nausea was the most common side effect that led to treatment discontinuation in clinical trials. The true incidence of sexual dysfunction is unknown; the long-term effects on body weight are also unknown. In clinical trials, treatment with duloxetine was associated with mean increases in BP averaging 2 mm Hg systolic and 0.5 mm Hg diastolic versus placebo. No studies have compared the BP effects of venlafaxine and duloxetine at equivalent therapeutic doses. Close monitoring is suggested when using duloxetine in patients who have or are at risk for diabetes. Duloxetine has been shown to increase blood sugar and hemoglobin A1C levels during long-term treatment. Patients with substantial alcohol use should not

be treated with duloxetine because of possible hepatic effects. It also should not be prescribed for patients with hepatic insufficiency and end-stage renal disease or for patients with uncontrolled narrow-angle

glaucoma. Abrupt discontinuation of duloxetine should be avoided because it may produce a discontinuation syndrome similar to that of venlafaxine. A gradual dose reduction is recommended. Clinicians should avoid the use of duloxetine by pregnant and nursing women unless the potential benefits justify the potential risks. Drug Interactions Duloxetine is a moderate inhibitor of CYP450 enzymes. Laboratory Interferences Data are not currently available on laboratory interferences with duloxetine. Dosage and Administration Duloxetine is available in 20-, 30-, and 60-mg tablets. The recommended therapeutic, and maximum, dosage is 60 mg per day. The 20- and 30-mg doses are useful for either initial therapy or for twice-daily use as strategies to reduce side effects. In clinical trials, dosages of up to 120 mg per day were studied, but no consistent advantage in efficacy was noted at doses higher than 60 mg per day. Duloxetine thus does not appear to demonstrate a dosage–response curve. However, there were difficulties in tolerability with single doses above 60 mg. Accordingly, when dosages of 80 and 120 mg per day were used, they were administered as 40 or 60 mg twice daily. Because of limited clinical experience with duloxetine, it remains to be seen to what extent dosages above 60 mg per day will be necessary and whether this will actually require divided doses to make the drug tolerable. MILNACIPRAN AND LEVOMILNACIPRAN Milnacipran is only FDA approved for the treatment of fibromyalgia. Although some countries have approved milnacipran for general use as an antidepressant, efficacy is not as well established. Compared with venlafaxine, milnacipran is approximately five times more potent for inhibition of norepinephrine uptake than for 5-HT reuptake inhibition. Milnacipran has a half-life of approximately 8 hours and shows linear pharmacokinetics between doses of 50 and 250 mg per day. Metabolized in the liver, milnacipran has no active metabolites. Milnacipran is primarily excreted by the kidneys. Milnacipran is available as 12.5-, 25-, 50-, and 100-mg tablets. The standard recommended milnacipran dose is as follows: day 1, 12.5 mg once daily; days 2 and 3, 12.5 mg twice daily; days 4 to 7, 25 mg twice daily; and day 7 and beyond, 50 mg twice daily. Levomilnacipran was approved in 2013 by the FDA as a treatment for major depressive disorder (MOD) in adults. Levomilnacipran is an active enantiomer of the racemic drug milnacipran. In vitro studies have shown that it has greater potency for

norepinephrine reuptake inhibition than for serotonin reuptake inhibition and does not directly affect the uptake of dopamine or other neurotransmitters. It is taken once daily as a sustained-release formulation. In clinical trials, doses of 40 mg, 80 mg, or 120 mg improved symptoms compared with placebo. The most common adverse reactions in the placebo-controlled trials were nausea, constipation, hyperhidrosis, increased heart rate, erectile dysfunction, tachycardia, vomiting, and palpitations. Rates of adverse events were generally consistent across the 40 to 120 mg dose range. The only dose-related adverse events were urinary hesitation and erectile dysfunction. REFERENCES Amsterdam JD, Wang CH, Shwarz M, Shults J. Venlafaxine versus lithium monotherapy of rapid and non-rapid cycling patients with bipolar II major depressive episode: A randomized, parallel group, open-label trial. J Affect Disord. 2009;112(1–3):219. Andrisano C, Chiesa A, Serretti A. Newer antidepressants and panic disorder: A meta-analysis. Int Clin Psychopharmacol. 2013;28(1):33–45. Frampton JE, Plosker GL. Duloxetine: A review of its use in the treatment of major depressive disorder. CNS Drugs. 2007;21:581. Kasper S, Corruble E, Hale A, Lemoine P, Montgomery SA, Quera-Salva M-A. Antidepressant efficacy of agomelatine versus SSRI/SNRI: Results from a pooled analysis of head-to-head studies without a placebo control. Int

Clin Psychopharmacol. 2013;28(1):12–19. Keller MB, Trivedi MH, Thase ME, Shelton RC, Kornstein SG. The Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT) Study: Outcomes from the 2-year and combined maintenance phases. J Clin Psychiatry. 2007;68:1246. Lam RW, Andersen HF, Wade AG. Escitalopram and duloxetine in the treatment of major depressive disorder: A pooled analysis of two trials. Int Clin Psychopharmacol. 2008;23(4):181. Lieberman DZ, Montgomery SA, Tourian KA, Brisard C, Rosas G. A pooled analysis of two placebo-controlled trials of desvenlafaxine in major depressive disorder. Int Clin Psychopharmacol. 2008;23:188. Liebowitz MR, Manley AL, Padmanabhan SK, Ganguly R, Tummala R. Efficacy, safety, and tolerability of desvenlafaxine 50 mg/day and 100 mg/day in outpatients with major depressive disorder. Curr Med Res Opin. 2008;24:1877. McIntyre RS, Panjwani ZD, Nguyen HT, Woldeyohannes HO, Alsuwaidan M. The hepatic safety profile of duloxetine: A review. Expert Opin Drug Metab Toxicol. 2008;4:281. Montgomery SA, Baldwin DS, Blier P, Fineberg NA, Kasper S. Which antidepressants have demonstrated superior efficacy? A review of the evidence. Int Clin Psychopharmacol. 2007;22:323. Nemeroff CB, Entsuah R, Benattia I, Demitrack M, Sloan DM. Comprehensive analysis of remission (COMPARE) with venlafaxine versus SSRIs. Biol Psychiatry. 2008;63:424. Owens MJ, Krulewicz S, Simon JS, Sheehan DV, Thase ME. Estimates of serotonin and norepinephrine transporter inhibition in depressed patients treated with paroxetine or venlafaxine. Neuropsychopharmacology. 2008;33:3201. Pae CU, Lim HK, Ajwani N, Lee C, Patkar AA. Extended-release formulation of venlafaxine in the treatment of posttraumatic stress disorder. Expert Rev Neurother. 2007;7:603. Papakostas GI, Fava M. A meta-analysis of clinical trials comparing milnacipran, a serotonin–norepinephrine reuptake inhibitor, with a selective serotonin reuptake inhibitor for the treatment of major depressive disorder. Eur Neuropsychopharmacol. 2007;17:32.

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