

Serotonin-Norepinephrine Reuptake Inhibitors

Jayakrishnan A V

EMS Co Operative Hospital & Research Centre, Perinthalmanna; Kerala Medical Journal*

ABSTRACT

Published on 24th September 2009

Serotonin-Norepinephrine reuptake inhibitors (SNRIs) are a class of antidepressant used in the treatment of major depression and other mood disorders. SNRIs were developed more recently than SSRIs, and there are relatively few of them. Their efficacy as well as their tolerability appears to be somewhat better than the SSRIs'. Abrupt discontinuation of SNRI- medication usually leads to a discontinuation syndrome which could include states of anxiety and further symptoms. The most common side effects include nausea, drowsiness, headache, changes in appetite, vivid dreams etc.

Keywords: Antidepressants, SNRI, Clinical uses

*See End Note for complete author details

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are a class of antidepressant used in the treatment of major depression and other mood disorders. They are also sometimes used to treat anxiety disorders, obsessive-compulsive disorder, attention deficit hyperactivity disorder (ADHD), chronic neuropathic pain and for the relief of menopausal symptoms. They act upon two neurotransmitters in the brain that are known to play an important part in mood, namely, serotonin and norepinephrine. This can be contrasted with the more widely-used selective serotonin reuptake inhibitors (SSRIs), which act mainly on serotonin.

Mode of action

Activity on norepinephrine reuptake is thought necessary for an antidepressant to be effective on neuropathic pain, a property shared with the older tricyclic antidepressants but not with the SSRIs. It has been theorized that depression corresponds with a reduction in communication and connectivity between neurons in the hippocampus. Neurons pass information to each other by means of neurotransmitters, which pass across the narrow synapses between the cells. After interacting with receptors on a postsynaptic neuron, most of the neurotransmitter is reabsorbed by the presynaptic cell in a process called reuptake. Antidepressants increase the number of neurotransmitters active in the synapse, thereby enhancing neuronal activity downstream. Via an effect on NMDA receptors, this causes neurogenesis and synapse formation which have been shown in animal models to correlate with the relief of depression.¹ Modern

antidepressants usually achieve this effect by blocking the transporter proteins that reabsorb certain neurotransmitters, hence the name "reuptake inhibitors." The result is that more of the neurotransmitter is left in the synaptic cleft, so it has a greater effect on the target neuron. SNRIs were developed more recently than SSRIs, and there are relatively few of them. Their efficacy as well as their tolerability appear to be somewhat better than the SSRIs', apparently owing to their compound effect. Discontinuation syndrome has been reported to be markedly worse for SNRIs when compared to SSRIs.

Adverse effects

As with the SSRIs, abrupt discontinuation of SNRI-medication usually leads to a discontinuation syndrome which could include states of anxiety and further symptoms. It is therefore recommended to slowly taper down the dose under the supervision of a psychopharmacologist when discontinuing SNRIs. Antidepressants including SNRIs have some dependence producing effects, most notably a withdrawal syndrome. However, their dependence producing properties are not as significant as benzodiazepines. For example antidepressants have less abuse potential than benzodiazepines.² Due to the effects of increased norepinephrine synaptic activity, these drugs are contraindicated in patients with hypertension, heart disease, or risk of stroke. Side effects and drug interactions

Because one of the actions of the SNRIs is to block the reuptake of serotonin as the SSRIs do, it has most

Corresponding Author:

Dr. Jayakrishnan A V, D. Ortho, M.S. Ortho, MCh (Neuro), Consultant Neuro & Spine Surgeon, EMS Co Operative Hospital & Research Centre, Perinthalmanna; Secretary, Kerala Medical Journal. Phone: 9847004064. Email: imakmj@yahoo.in

of the same side effects. The most common include nausea, drowsiness, headache, changes in appetite, vivid dreams, and sexual side effects. There are two common sexual side effects: diminished interest in sex (libido) and difficulty reaching climax (orgasm), which are often milder on SNRIs than SSRIs. Nonetheless, sexual side effects account for a large amount of drug discontinuations with both SSRIs and SNRIs.

Activity at the norepinephrine transporter can sometimes cause anxiety, mildly elevated pulse, and elevated blood pressure; people at risk for hypertension and heart disease should have their blood pressure monitored.

SNRIs should be taken with caution when using St John's wort and should never be taken within 14 days of an MAOI antidepressants.

SNRIs currently available venlafaxine was the first and most commonly used SNRI. While it primarily affects the reuptake of serotonin and norepinephrine, it also blocks the reuptake of dopamine at doses above 150mg. desvenlafaxine⁴ is the active metabolite of venlafaxine and is believed to work in the same manner, though some evidence suggests lower response rates compared to venlafaxine and duloxetine. It was introduced in May 2008. duloxetine also inhibits serotonin reuptake and has been approved for the treatment of depression and neuropathic pain in August 2004. Duloxetine is contraindicated in patients with heavy alcohol use or chronic liver disease, as duloxetine can increase the levels of certain liver enzymes which can lead to acute hepatitis or other diseases in certain at risk patients. Currently, the risk of liver damage appears only to be for patients already at risk, unlike nefazodone, which can rarely cause damage to the liver in health patients.

sibutramine is an SNRI which failed to show antidepressant activity in animal tests, but instead has been widely marketed as an appetite suppressant drug for weight loss.

nefazodone an antidepressant with efficacy similar to SSRIs, but without the sexual side effects. In fact, Serzone at times may act similarly to Wellbutrin in its neutral or at times positive effect on function. It has been discontinued in several countries due to cases of liver failure. The tradename "Serzone" has been discontinued, but generic nefazodone is currently available. However, the liver failure is rare, and a simple blood test every 6 months to assess liver enzyme levels is

sufficient. Nefazodone has an active metabolite which at higher doses (> 250 mg/day) can increase anxiety.

milnacipran has shown to be significantly effective in the treatment of depression and Fibromyalgia syndrome (FMS). The Food and Drug Administration (FDA) approved milnacipran for treatment of Fibromyalgia in the United States in January 2009. Milnacipran has been commercially available in Europe and Asia for several years.

bicifadine inhibits the reuptake of serotonin and norepinephrine (and dopamine to a lesser extent) but rather than being developed for the already crowded antidepressant market, it is being researched as a non-opioid, non-NSAID analgesic drug.

Serotonin-norepinephrine-dopamine-reuptake-inhibitors (SNDRI) are a class of psychoactive antidepressants. They act upon neurotransmitters in the brain, namely, serotonin, norepinephrine and dopamine. These three biogenic monoamines are associated with depression and increasing the availability in the brain is one method used to treat the condition.

SNDRI are so-called triple reuptake inhibitors (TRIs), which elevate extracellular plasma concentrations of all three monoamine neurotransmitters, serotonin, norepinephrine and dopamine in the synaptic cleft. These compounds show high potency but low selectivity between the different monoamine transporter proteins. No SNDRI are yet on the market, although the first of these agents tesofensine is currently in clinical trials and other compounds such as brasofensine³ and GlaxoSmithKline's NS2359 are under development.

It should be noted that some SNRI drugs such as Venlafaxine and Sibutramine are known to weakly inhibit the reuptake of dopamine at high doses, and so while these drugs are selective for the serotonin and noradrenaline transporters at normal doses, they can start to act as SNDRI when taken at doses above the normal therapeutic range.

END NOTE

Author Information

Dr. Jayakrishnan AV, D. Ortho, M.S. Ortho, MCh (Neuro), Consultant Neuro & Spine Surgeon, EMS Co Operative Hospital & Research Centre, Perinthalmanna

Conflict of Interest: None declared

Cite this article as : Jayakrishnan A V. Serotonin-Norepinephrine Reuptake Inhibitors. Kerala Medical Journal. 2009 Sep 24;2(3):96-98

REFERENCES

1. Reid IC, Stewart CA. How antidepressants work: new perspectives on the pathophysiology of depressive disorder. *Br J Psychiatry*. 2001 Apr;178:299–303.
2. van Broekhoven F, Kan CC, Zitman FG. Dependence potential of antidepressants compared to benzodiazepines. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002 Jun;26(5):939–43.
3. Karch, Amy (2006). 2006 Lippincott's Nursing Drug Guide. Philadelphia, Baltimore, New York, London, Buenos Aires, Hong Kong, Sydney, Tokyo: Lippincott Williams & Wilkins. ISBN 1-58255-436-6.
4. Deecher DC, Beyer CE, Johnston G, Bray J, Shah S, Abou-Gharbia M, et al. Desvenlafaxine succinate: A new serotonin and norepinephrine reuptake inhibitor. *J Pharmacol Exp Ther*. 2006 Aug;318(2):657–65.
5. Iyengar S, Webster AA, Hemrick-Luecke SK, Xu JY, Simmons RM (November 2004). "Efficacy of duloxetine, a potent and balanced serotonin- norepinephrine reuptake inhibitor in persistent pain models in rats". *J. Pharmacol. Exp. Ther.* 311 (2): 576–84.
6. Nonogaki K, Nozue K, Kuboki T, Oka Y. Milnacipran, a serotonin and norepinephrine reuptake inhibitor, induces appetite-suppressing effects without inducing hypothalamic stress responses in mice. *Am J Physiol Regul Integr Comp Physiol*. 2007 May;292(5):R1775–81.