

## Vortioxetine (Trintellix) The new antidepressant



Vortioxetine has been approved for use in major depressive disorder in Canada. Vortioxetine works on several different serotonin receptors and transporters as well as norepinephrine and dopamine transporters. Vortioxetine has been shown to be more effective than placebo in several trials. It has been shown to be effective in patients who had previously failed a course of a serotonin norepinephrine reuptake inhibitor (SNRIs) or a selective serotonin reuptake inhibitor (SSRIs) for major depressive disorder. Vortioxetine can be nauseating and to minimize this side-effect it is important to start on a low dose and increase the dosage slowly over several weeks.

**Vortioxetine may improve cognition (processing speed, verbal learning and memory) and it can be used in depressed patients whose cognitive abilities have been declining to try to improve them.** As with SSRIs and SNRIs, vortioxetine can cause hyponatremia and this risk is greatest in the elderly receiving diuretics. For this reason sodium levels should be monitored when a patient is initiated on vortioxetine. Currently Vortioxetine is not covered by ODB, it costs around \$100 per month for treatment.

### Antidepressant Use in the Elderly

Antidepressants are commonly used in patients who are in long term care (LTC) centers. These medications can be used in a variety of ways for different symptoms. The most common uses are depression, anxiety, agitation and insomnia. This newsletter will highlight some of the more nuanced uses of antidepressants. Antidepressants and anxiolytic (anti-anxiety) medications act on neurochemicals or neurotransmitters in the brain. The most common neurotransmitters that are targets of antidepressant activity are serotonin, norepinephrine (or noradrenaline), dopamine and histamine. Each neurotransmitter has its own unique therapeutic effects. Table 1 lists the different neurotransmitters, the drug classes that target those transmitters and their therapeutic effect.

#### Therapeutic action of various neurotransmitters <sup>[1]</sup>

| Neurotransmitter | Drug classes targeting transmitter  | Therapeutic Action  |
|------------------|---|---|
| Serotonin        | <ul style="list-style-type: none"> <li>▪ Selective serotonin reuptake inhibitors (SSRIs).</li> <li>▪ Serotonin norepinephrine reuptake inhibitors (SNRIs)</li> <li>▪ Trazodone</li> <li>▪ Mirtazapine</li> <li>▪ Tricyclic antidepressants</li> </ul> | Antidepressant and anxiolytic (anti-anxiety) effects                          |
| Norepinephrine   | <ul style="list-style-type: none"> <li>▪ SNRIs</li> <li>▪ Mirtazapine</li> <li>▪ Tricyclic antidepressants (TCA)</li> </ul>   | Antidepressant effects. Some SNRIs and TCAs can also be used for chronic pain |
| Dopamine         | <ul style="list-style-type: none"> <li>▪ SNRIs</li> <li>▪ Bupropion</li> <li>▪ Antipsychotics</li> </ul>  | Antipsychotic and antidepressant effects                                      |
| Histamine        | <ul style="list-style-type: none"> <li>▪ Trazodone</li> <li>▪ Mirtazapine</li> <li>▪ Tricyclic antidepressants</li> </ul>   | Anxiety and Insomnia  |

Antidepressants have different levels of action on different neurotransmitters. Table 2, highlights the different potencies of several antidepressants. This table is meant to illustrate that even though two antidepressants may be from the same medication family (for example, both antidepressants may be SSRIs), their activity on a neurotransmitter may be quite different. For example, Cipralex has little effect on increasing norepinephrine, where as Paxil has significantly greater effect on increasing norepinephrine. Due to the large difference in antidepressants' activity on neurotransmitters, this means that a patient may experience very different results from different antidepressants in the same medication family.

### Relative Potencies for Norepinephrine, Serotonin and Dopamine Blockade <sup>[2]</sup>

| Medication                | Serotonin | Norepinephrine | Dopamine |
|---------------------------|-----------|----------------|----------|
| <b>SSRIs</b>              |           |                |          |
| Citalopram (Celexa)       | ++++      | +              |          |
| Escitalopram (Cipralex)   | ++++      | +              |          |
| Fluoxetine (Prozac)       | +++       | ++             | +        |
| Fluvoxamine               | ++++      | ++             |          |
| Paroxetine (Paxil)        | ++++      | +++            | ++       |
| Sertraline (Zoloft)       | ++++      | ++             | +++      |
| <b>SNRIs</b>              |           |                |          |
| Venlafaxine (Effexor)     | ++++      | +++            | +        |
| Desvanlafaxine (Pristiq)  | +++       | +              | +        |
| Duloxetine (Cymbalta)     | ++++      | ++++           | ++       |
| Vortioxetine (Trintellix) |           |                |          |
| <b>Aminoketone</b>        |           |                |          |
| Bupropion (Wellbutrin)    | 0/+       | +              | ++       |
| <b>Triazolopyridines</b>  |           |                |          |
| Trazodone                 | ++        | 0              |          |
| <b>Tricyclics</b>         |           |                |          |
| Desipramine (Norpramin)   | +         | ++++           |          |
| Nortriptyline (Pamelor)   | ++        | +++            |          |
| Amitriptyline (Elavil)    | ++++      | ++++           |          |
| Imipramine (Tofranil)     | +++       | ++             |          |
| Doxepine (Sinequan)       | +++       | +              |          |
| <b>Tetracyclics</b>       |           |                |          |
| Mirtazapine (Remeron)     | +++       | ++++           | 0        |

**Level of drug activity on receptor:** 0 = negligible    + = very low    ++ = low    +++ = moderate    ++++ = high

Depending on the symptoms that the patient is experiencing, the type of medication used can target those symptoms based on the neurotransmitters the medication affects. For example, a patient experiencing depression and neuropathic pain could be started on an SNRI (such as Cymbalta/duloxetine) to treat both the depression and the pain.

It should be noted that when an antidepressant is started for depression or anxiety it normally takes 4-6 weeks before the patient will notice the effect of the medication on their depression or anxiety. It is important that patients understand this when starting an antidepressant so that they do not get discouraged and discontinue their antidepressant if they do not see improvements in their symptoms after the first few weeks of use.

## Using Antidepressants for Insomnia and Agitation

Trazodone is used in low to moderate doses (< 150 mg /day) for insomnia and for agitation. At these doses it has little effect on depression and it works primarily on the histamine receptors, causing drowsiness, and adrenergic (alpha1) receptors, which reduces agitation <sup>[1]</sup>.

Quetiapine, an antipsychotic, is used in low doses ( $\leq 50$  mg/day) not for its effects on mood but for its sedating effect. Low doses of quetiapine act primarily on histamine receptors. For this reason, low doses of quetiapine are used primarily for sleep or agitation. It should be noted that the use of antipsychotics should be minimized in the elderly with dementia due to an increased risk of death when compared with placebo. Most deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia). Due to this risk, all antipsychotics carry a black-box warning regarding use in elderly patients with dementia.

Similarly, low doses of mirtazapine ( $\leq 15$  mg per day) are not used for depression, but for their sedating effects for insomnia.

## Side-Effects of Antidepressants

Antidepressants can have many potential side effects. The most commonly experienced side-effects are headache, dizziness, dry mouth, drowsiness or insomnia, nausea, and fatigue. Often these side-effects improve after several weeks of medication use. Weight gain can occur due to antidepressant use. The usual weight gain reported in studies is relatively modest with most SSRIs showing weight gain between 2-10 lbs <sup>[3]</sup>.

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*Weight loss can occur with bupropion. Amitriptyline, imipramine and mirtazapine are the antidepressants that cause the most weight gain.*

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Sexual dysfunction (decreased libido or reduced pleasure from sex) can also occur. Bupropion has been shown to have less sexual dysfunction than other antidepressants.

## Drug interactions

When SSRIs and SNRIs are combined with anti-inflammatories (such as ibuprofen or naproxen) and/or anticoagulants (such as warfarin, rivaroxaban, dabigatran and apixaban) there is an increased risk for GI bleeding. It is thought that SSRIs and SNRIs may enhance the antiplatelet properties of NSAIDs and anticoagulants. In elderly patients taking NSAIDs or anticoagulant and an SSRI or SNRI who are frail or have a history of previous GI bleeds or ulcers should be given a PPI for prophylaxis.

Most antidepressants can prolong the QT interval and when they are combined with QT prolonging agents the effect can be magnified. The QT interval is measured with an EKG, and if it is prolonged it increases the patient's risk for developing life threatening arrhythmias. For patients taking QT prolonging agents who are started on an antidepressant, their QT interval should be monitored. A QT corrected for heart rate (QTc) above 500 ms is considered to be dangerous and actions should be taken to discontinue or change some of the medications prolonging the QT interval.

## Medications to Avoid in the Elderly

Tri-cyclic Antidepressants (TCAs) (e.g. Elavil/amitriptyline) are generally avoided in the elderly due to their side-effects. TCAs are known to cause anticholinergic side-effects such as: constipation, urinary retention, dry mouth, and blurred vision. TCAs are also sedating and should be given in the evening for this reason. Most people (elderly or non-elderly) are unable to tolerate TCAs at high enough doses for them to be effective as antidepressants. Because of this, TCAs are generally avoided for depression, but they can be effectively used in low doses for neuropathic pain or insomnia. Nortriptyline (Aventyl) is the TCA of choice in the elderly as it has the least anticholinergic side-effects.

Benzodiazepines (e.g. Ativan/lorazepam) are avoided for the treatment of depression as they can worsen depressive symptoms, cause side-effects such as confusion and sedation and increase risk of falls in the elderly. Benzodiazepine tolerance can develop and discontinuing benzodiazepines can lead to withdrawal symptoms for patients who have been using them regularly for several weeks or months. Benzodiazepines can be used effectively for the treatment of anxiety or insomnia, but they are generally avoided in the elderly due to the increase risk of falls and the risk of dependence.

## Hyponatremia with SSRIs and SNRIs:

In elderly patients, there is a risk of SSRIs and SNRIs causing hyponatremia (low sodium levels), especially in those taking diuretics. Antidepressant induced hyponatremia can occur after only a few weeks of antidepressant use. The potential symptoms of hyponatremia include nausea and vomiting, confusion, fatigue, restlessness, irritability, and seizures. These symptoms can be very similar to those of a UTI in a patient with dementia. Because of this, sodium levels should be monitored when a patient is started on a SSRI/SNRI or their dosage is increased and, once the patient has been stabilized on an SSRI/SNRI, sodium levels should be routinely monitored thereafter. Sodium levels should be done 1-2 weeks after initiating an antidepressant and then repeated every 3-6 months with routine blood work. Mirtazapine and bupropion are associated with lower instances of hyponatremia, and these agents should be considered in patients at greater risk of experiencing hyponatremia (such as those on diuretics, frail individuals and those with low baseline sodium levels).

## Treatment Failure with SSRIs and SNRIs

For patients who experience treatment failure for depression on an SSRI or SNRI after the dose of the SSRI or SNRI has been increased to target ranges, we can consider adding bupropion to the SSRI/SNRI. When bupropion is added to an SSRI or SNRI we are trying to increase norepinephrine and dopamine activity, in addition to the serotonin increase from the SSRI/SNRI, to provide triple action on neurotransmitters. For patients taking an SNRI we can consider adding mirtazapine. When adding mirtazapine, we are attempting to increase the serotonin and norepinephrine levels in the patient.

Alternatively, for patients who experience treatment failure with an SSRI or an SNRI, switching to a new SSRI or SNRI may be effective in achieving remission of depression.

Within a class there is a lot of inter-individual variability of effectiveness of medications and sometimes switching to a different medication in the same class can achieve remission. According to the STAR\*D study, one in four patients achieved remission of their symptoms after switching to a different antidepressant. In patients with treatment resistant depression, vortioxetine would be a good alternative to try.

## Summary

Antidepressants are used to treat a variety of conditions, the most common being depression and anxiety. Antidepressants should be the first choice for depression and anxiety over benzodiazepines. Antidepressants all have their own unique action and there is a lot of variation of effects between antidepressants in the same class. Each patient responds to antidepressants differently and it is possible that one patient may find an antidepressant effective and another patient may find the same antidepressant ineffective.

## References

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