Graylands Hospital

DRUG BULLETIN

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Reboxetine – a 'NaRI'

Graylands Hospital Drug Bulletin 2002 Vol 10 No3 November ISSN 1323-1251

Where is its place in therapy?

- There is no convincing evidence to suggest an overall advantage in efficacy, relapse prevention or speed of onset with reboxetine over existing antidepressants.
- It may be useful in SSRI resistant depression. More evidence is needed to support its use in indications such as anxiety, OCD and panic disorder.
- Noradrenergic deficiency differs to serotonergic deficiency and is associated with impaired attention, problems concentrating, fatigue and memory deficits. These symptoms may respond best to treatment with a selective noradrenergic agent, such as reboxetine.
- Like the SSRIs, reboxetine offers advantages over the tricyclics and the MAOIs in terms of safety.
- Unlike the SSRIs & TCAs it does not significantly interact with cytochrome P450 enzymes.
- Reboxetine is associated with "pseudo-anticholinergic" symptoms (not due to direct action on cholinergic receptors). This may preclude its use in certain patients.

Reboxetine (Edronax®) is the latest addition to the choice of antidepressants available on the PBS in Australia. It is indicated for the treatment and prevention of relapse of major depression. So what advantages, if any, does it offer over existing agents?

Mode of action

Reboxetine is the first selective noradrenaline reuptake-inhibitor ("NaRI") to be introduced and has only a weak effect on serotonin reuptake and no effect on dopamine uptake. It has no significant affinity for cholinergic or adrenergic receptors, however this is not necessarily reflected in its side-effect profile.

Pharmacokinetics

Reboxetine is well-absorbed following oral administration and can be taken without regard to food. Cytochrome P4503A4 is primarily responsible for the hepatic metabolism of reboxetine; the major metabolite is inactive. It is a weak inhibitor of CYP3A4 and CYP2D6 (not thought to be clinically relevant when used within recommended dose range). The half-life is approximately 12 hours (consistent with twice daily dosing) and excretion is mainly via the renal route.

Efficacy

Depression

Short-term trials have shown reboxetine to be more effective than placebo [1,2,3,4] and similarly effective to fluoxetine [4,5], imipramine [6,7] and desipramine [1] in the treatment of major depression. In a subset of severely depressed patients, reboxetine was significantly more effective than fluoxetine[5].

In a long-term study (up to 1 yr), reboxetine demonstrated superior efficacy to placebo in prevention of relapse and recurrence of depression [3]. At the 12 month assessment, 78% of patients treated with reboxetine were classified as in remission, compared with 45% of patients in the placebo group.

Reboxetine is not on the hospital formulary as yet.

Social functioning

Claims are also made regarding significant improvement in social interaction and functioning compared with fluoxetine [8]. However, this is based on trials using a less complex questionnaire [9] which was recently developed and validated by the manufacturer. This result requires confirmation, ideally with the use of established scales.

Other areas

Core symptoms of depression, such as anxiety and agitation, can often be exacerbated by antidepressants. A pooled analysis found that reboxetine was not associated with an increased incidence of treatment-emergent anxiety or agitation [10]. Patients who suffered from generalised anxiety disorder were excluded from these trials, so these findings may not extend to *treatment* of these patients.

Small studies have shown potential for the use of reboxetine in panic disorder [11,12], Parkinson's Disease [13,14] and possibly bulimia [15] (though constipation may reduce its suitability in this area). More evidence is needed to support its use in these situations.

When NOT to use reboxetine

The use of reboxetine in conjunction with MAOIs is not recommended. The manufacturer also contraindicates its use in patients with narrow angle glaucoma due to its weak mydriatic effect.

When to use reboxetine with CAUTION

Similarly to other antidepressants, reboxetine carries a warning with regard to its use in patients with a history of epilepsy.

The possibility for a switch to mania/hypomania exists, especially in patients with bipolar disorder. A literature report [16] describes the emergence of hypomanic symptoms in 3 bipolar patients within 2-4 weeks of starting reboxetine.

A review of the tolerability of reboxetine states that symptoms related to hypotension or tachycardia may be experienced by up to 10% of patients who receive the drug. It should be used with caution and close supervision in patients with cardiac disease and/or taking antihypertensives[17]. Orthostatic hypotension is more common at doses higher than the maximum recommended.

Reboxetine should be used with caution in men with prostatic enlargement (see below).

Is it safe to use in pregnancy and breastfeeding?

Pregnancy - Category B1. Information regarding exposure to reboxetine during pregnancy is limited. A few cases are described in the literature but insufficient information is available to make an assessment of safety [17].

The use of reboxetine whilst breastfeeding is not recommended. A literature search revealed no case reports.

Side effect profile

Adverse events that occurred significantly more frequently with reboxetine than placebo are summarised in Table 1.

Reboxetine is mostly associated with anticholinergic-type symptoms. This is not due to direct blockade of cholinergic receptors but to indirect reduction of net parasympathetic tone, resulting from increased sympathetic tone. They are probably more of a nuisance than a danger, and will generally subside with time. However, they may be significant enough to cause discontinuation in a number of patients.

In general, reboxetine was better tolerated than imipramine and desipramine. Compared to fluoxetine, reboxetine was associated with a higher incidence of anticholinergic-type effects, such as dry mouth and constipation but less SSRI-type events such as diarrhoea and nausea [17,18].

Table 1: Placebo-controlled trials – incidence (%) of adverse effects [17,18]

SIDE EFFECT	REBOXETINE	PLACEBO
Dry mouth	27	16
Constipation	17	8
Increased sweating	14	7
Insomnia	14	5
Urinary hesitancy	5	2
Impotence	5	0
Tachycardia	5	2

Sexual dysfunction appears to be dose-related (doses of >8mg). Urinary hesitation/retention occurred more frequently in males than females in long-term studies. It may be

advisable to avoid reboxetine in men with prostatic enlargement [17].

Short and long term studies in the elderly and adults showed that reboxetine treatment induced rhythm abnormalities more frequently than imipramine and placebo (sinus tachycardia being the most frequently observed abnormality)[19,20]. Reboxetine was also associated with occasional atrial and ventricular ectopic beats in the elderly. Treatment emergent conduction abnormalities in the elderly were mostly left anterior hemiblock.

A study by the manufacturer to examine the effect of reboxetine on cardiac repolarisation in 20 healthy subjects, found no statistically significant prolongation of the QTc interval, at exposures of up to twice the recommended dose [21].

A case report of hyponatremia in association with reboxetine (occurred again upon rechallenge) has been published [22].

Dosage and administration

Recommended starting dose is the therapeutic dose: 4mg twice daily, increasing to 10mg daily if necessary after 3 weeks.
Elderly: 2mg twice daily, increased to 6mg daily if necessary after 3 weeks.
Renal/hepatic impairment: start at 2mg twice daily and increase according to patient tolerance.

Switching to and from reboxetine

No specific data regarding this issue could be found. The following are recommendations only.
Switching to reboxetine: A 14 day drug-free gap is required when switching from MAOIs. With other agents, a careful cross-taper may be appropriate. Caution is required with nefazodone/fluvoxamine and fluoxetine (due to CYP3A4 inhibition and a long elimination half-life respectively).
Switching from reboxetine: At least a week's drug-free interval should be allowed before MAOIs (and possibly moclobemide) are commenced.

Combination with other antidepressants

Reboxetine has been used in combination with SSRIs[17,23,24] and mirtazapine [17] to treat resistant depression with some success. It may be favoured over TCAs as a noradrenergic agent due to reduced potential for drug interaction and better tolerability. **Combination strategies are not recommended and should only be undertaken with caution and when other treatment options have failed.**

Drug Interactions

Compounds that inhibit CYP3A4 may *increase* the plasma levels of reboxetine. These include ketoconazole, itraconazole, clarithromycin, erythromycin, fluvoxamine nefazodone and cimetidine. Carbamazepine may induce the metabolism of reboxetine, resulting in *lower* plasma levels. The doses of reboxetine may need to be adjusted accordingly. Reboxetine appears to have little effect on the activity of other major isoenzymes.

The use of reboxetine and lithium has not been specifically evaluated. Due to minimal glomerular filtration of unbound reboxetine, no effect on lithium elimination is expected. However, the manufacturers recommend monitoring of the lithium level.

Use with ergot derivatives (in some migraine preparations) may result in increased blood pressure.

Reboxetine does not interact with alcohol [25].

ADVERSE EFFECT	ASSOCIATION WITH REBOXETINE?
Insomnia	Treatment emergent insomnia may be problem. May settle after a few weeks of therapy.
Agitation/anxiety	Incidence similar to placebo in short-term studies.
Discontinuation syndrome	Potential association due to short half-life. However symptoms were not evident upon abrupt discontinuation in clinical trial programme.
Weight gain	Not associated with weight gain.
Anticholinergic effects	May be a problem but in general less than TCAs. Urinary hesitation/retention occurred more often in males; avoid in men with prostate enlargement.
Nausea/diarrhoea	Incidence less than with SSRIs.
Sexual dysfunction	Impotence and reduction in libido more common at doses >8mg/day.

Clinical conditions and the suitability of reboxetine

CONDITION	COMMENT
Elderly	Caution - anticholinergic/cardiovascular effects (treatment emergent rhythm / conduction abnormalities). SSRI probably safer. Dose: 2mg bd, max 6mg/day.
Hepatic/renal dysfunction	Use half recommended therapeutic dose (2mg bd). Increase according to patient tolerance.
Cardiac dysfunction	Symptoms related to tachycardia and hypotension may be experienced by up to 10% patients. Use with caution in patients with cardiac disease/taking antihypertensives. Orthostatic hypotension more common at higher doses. SSRI probably preferable.
Concomitant medications Risk of drug interactions	Low risk - little interaction with CYP450 system. Caution with drugs that potently inhibit CYP3A4. See drug interactions section.
Pregnancy/lactation	Pregnancy category B1. Limited information and clinical experience available. Not recommended.
Toxicity in overdose	Limited data available suggest lack of toxicity in overdose. However, more information and clinical experience required before relative safety can be confirmed.
Anxiety disorder	No evidence to support use in generalised anxiety disorder.
Panic disorder & OCD	Use SSRIs first-line. Reboxetine may be useful in SSRI-refractory panic disorder [12]. No evidence for use in OCD.
Epilepsy	Rare reports of seizures in clinical trials. Start with low dose and titrate slowly.
Chronic pain	No evidence to support its use in this area at present.
Parkinson's disease	A small study and case report have suggested its potential use [13,14]. Lack of effect on dopamine may be beneficial.

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Presentation

Available as 4mg scored tablet. Manufacturer: Pharmacia.

Antidepressant	Daily dose (mg)	Hospital cost (A$) per 28 days
Reboxetine	8	29.71
Paroxetine	20	23.89
Fluoxetine	20	3.12
Sertraline	100	26.96
Citalopram	20	20.22
Fluvoxamine	100	24.30
Mirtazapine	30	24.61
Venlafaxine XR	150	38.78

Acknowledgement

This article was prepared by Kate Smith and reviewed by members of the Pharmacy Department.

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