Reboxetine: A Novel Antidepressant

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Depression is a common and disabling disorder. The World Health Organisation has ranked depression fourth in a list of the most urgent health problems worldwide. Depression has major effects on economic productivity, individual well being and social functioning, around the globe. It is a huge burden on individuals, families, and society. The lifetime risk for major depression has been estimated to be 7%-12% for men and 20%-25% for women.

According to the Biogenic Monoamine theory of Schildkraut (1965), depression results due to impairment or dysregulation of aminergic transmission. Others suggest that though noradrenaline and serotoninergic systems are involved, the specific impairment that underlies depression is unclear and is likely to vary among patients.

Medical treatment for depression favors prescription antidepressant drugs that work by increasing neurotransmission for one or more of the monoamines—serotonin, norepinephrine, or dopamine. Before 1980, antidepressant treatment consisted primarily of the tricyclic antidepressants (TCADs), monoamine oxidase inhibitors (MAOI), and lithium. The antidepressant properties of these medications are attributed to modulation of noradrenergic and serotonergic function, but they also have many side effects due to binding to multiple unrelated receptors. The tricyclics antagonize muscarinic, H, histaminic, and α adrenergic receptors causing constipation, urinary retention, dry mouth, sedation, and postural hypotension. In addition to these, the monoamine oxidase inhibitors have the added risk of potentially severe hypertensive crisis due to pressor effects of dietary tyramine, which requires dietary restrictions. This risk is much lower with the newer reversible inhibitors of monoamine oxidase. Both the tricyclics and the monoamine oxidase inhibitors can be lethal in overdose, and the monoamine oxidase inhibitors interact dangerously with several over the counter and prescription drugs.

In the late 1980’s a important class of antidepressant was introduced, the selective serotonin reuptake inhibitors (SSRIs), which includes fluvoxamine, fluoxetine, sertraline, paroxetine, and citalopram. This class has become a mainstay of antidepressant treatment because of substantial advantages over the tricyclics and monoamine oxidase inhibitors in safety, tolerability, and ease of dosing. The SSRI’s also have limitations, especially response failure in many of those most severely affected. Many patients experience side effects like gastrointestinal complaints, nervousness and agitation, sexual dysfunction, and weight gain with long term use.

All these lead to difficulty in long term treatment and non compliance. Hence, one of the most important goals in the pharmacological treatment of depression is to provide the patients with highly efficacious drugs that have few side effects, low or no toxicity and a high level of tolerability.

Reboxetine is a selective noradrenaline reuptake inhibitor (NaRI), the first drug of new antidepressant class introduced in 1997. Reboxetine is a α-ariloxybenzyl derivative of morpholine.

Mechanism of Action
Reboxetine is a selective inhibitor of noradrenaline reuptake. It inhibits noradrenaline reuptake invitro to a similar extent to the tricyclic antidepressant desmethylimipramine. Reboxetine does not affect dopamine or serotonin reuptake and it has low in vivo and invitro affinity for adrenergic, cholinergic, histaminergic, dopaminergic and serotoninergic receptors.

Pharmacokinetic Properties
Reboxetine is rapidly and extensively absorbed following oral administration. Maximum plasma concentration of reboxetine is reached in 2-2.5 hours after a 4 mg oral dose in healthy volunteers. Reboxetine has linear pharmacokinetics across the normal dose range. Steady state plasma concentrations are reached within 5 days of starting therapy. Reboxetine is 98 % bound to plasma proteins, predominantly the α, acid glycoprotein. Reboxetine is metabolized by dealkylation, hydroxylation and oxidation followed by glucuronide or sulfate conjugation. It is metabolized by the cytochrome P450 CYP isoenzyme 3A4. Compounds that decrease the activity of this isoenzyme are likely to increase the plasma concentrations of reboxetine. Reboxetine has a relatively short elimination half life of 12.5 hours and therefore is given twice daily. Elimination is mainly via urine with 10% excreted as unchanged drug. Elderly individuals, patients with hepatic and renal insufficiency have a higher plasma concentration, a longer t1/2, and reduced clearance of reboxetine.

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Dose
Initial dose for adults is 4 mg twice daily. For most patients an increase in dose is not necessary. However, if needed, the dose may be increased to a total of 10-12 mg/day in two doses after 3 weeks. In elderly patients or those with hepatic or renal impairment, therapy may be initiated at 2 mg twice daily and increased to a maximum of 6 mg/day in two doses after 3 weeks.2,5

ADRs
Due to selectivity of reboxetine for norepinephrine, it is generally well tolerated with a benign side effect profile. The side effects reported are dry mouth, constipation, urinary hesitancy and/or retention and other anticholinergic side effects; CNS side effects like agitation, anxiety, nervousness, day time somnolence. A small percentage of patients have reported sexual dysfunction.2,5,7

Drug Interactions
Clinical data on interactions with reboxetine is limited, but concomitant administration with MAO inhibitors, tricyclic antidepressants, SSRIs, antipsychotics, antiarrhythmics, cyclosporin, azole antifungals, and macrolide antibiotics5,7 should be avoided.

Comparison of Efficacy with other antidepressants
In clinical trials, Reboxetine has been shown to be at least as effective as tricyclic antidepressants desipramine and imipramine in the treatment of patients with major depressive disorder in the adult and the elderly population and offers a significant advantage over imipramine in the treatment of melancholic patients.5,8

Reboxetine is as effective as SSRI fluoxetine.8,9 Reboxetine offers significant advantages over fluoxetine in terms of social functioning. Certain symptoms within the depressive syndrome respond better to NaRIs, whereas other symptoms respond better to SSRIs. Noradrenergic neurons are involved in mood, arousal, appetite, reward and drives. Dopamine is important for pleasure, sex, psychomotor activity; Serotonin in regulatory control of affects, aggression, sleep and appetite. Norepinephrine depletion studies suggest that while norepinephrine reuptake inhibition may improve all core symptoms of depression, norepinephrine regulation may be most closely correlated with patient improvements in energy, interest, concentration, agitation, helplessness, and hopelessness. Reboxetine, therefore, through its mechanism of action may be useful for drive deficient anergic states5 where the capacity for sustained motivation is lacking; for melancholic depressives with a poor ability to cope with stress;8 and those with comorbid anxiety.2 In a sub-analysis of patients with severe depression indicated that, reboxetine had superior efficacy compared with fluoxetine.8,10 Remission rates were similar for reboxetine, imipramine and fluoxetine. The onset of action 2-3 weeks is similar to other antidepressants.5

Comparison of Safety & Tolerability with other antidepressants
Reboxetine has a significantly improved adverse event profile as compared to TCADs.8 When compared with imipramine, in patients with severe depression and melancholy the frequency of discontinuation due to adverse events was lower in the reboxetine-treated and the cumulative risk of development of dry mouth, hypotension and/or related symptoms and tremor was significantly higher on imipramine than on reboxetine.11 Data from patients treated with reboxetine show that reboxetine has no significant cardiovascular effects, a low potential for drug interactions, causes no significant impairment of cognitive or motor function and no increase in suicidal ideation. In contrast to certain serotonergic drugs, there is no evidence of any withdrawal syndrome upon abrupt discontinuation or tapering of reboxetine treatment. Sexual dysfunction appears in only a small fraction of the patients and mainly with doses higher than 8 mg daily.12

Elderly patients are particularly susceptible to the potential side effects of current antidepressants due to age related physiologic changes. Reboxetine 4 mg/day, increasing to 6 mg/day on the basis of individual patient tolerability, may be considered safe dose range for testing the efficacy and tolerability of reboxetine in long term controlled clinical trials in elderly patients with depression.13

Other indications
Reboxetine has been found useful in narcolepsy,14 Panic disorders,15 treatment of depression in patients with Parkinsons disease.16

Conclusion
Noradrenaline has a major impact on the symptomatology of depression. It is involved in enhancing vigilance, attention, and drive. The determination of outcome of treatment of depression is important both for the symptoms of depression and social functioning.17 Hence, noradrenaline reuptake inhibitors may have a greater impact on drive, motivation, energy and social functioning. A comprehensive series of clini-
cal trials have compared the unique selective NaRI reboxetine with placebo and with the TCADs imipramine and desipramine, as well as with the SSRI fluoxetine. Reboxetine is clearly effective in both the short and the long term compared with placebo. Against comparator antidepressants, reboxetine is at least as effective in the treatment of patients with major depressive disorder in the adult and the elderly population and offers a significant advantage over imipramine in the treatment of melancholic patients. It has a significantly improved adverse event profile compared with TCADs. In severely depressed patients, reboxetine was significantly more effective than fluoxetine. Reboxetine also offers significant advantages over fluoxetine in terms of social functioning.8,18

Reboxetine, the first selective NaRI, with its selective mechanism of action, offering equivalent or even better efficacy in certain patient groups and acceptable tolerability profile is a valuable addition to the existing armamentarium of drugs used for the treatment of depression.

References


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