Chairman's Overview

The Place of Reboxetine in Antidepressant Therapy

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A wide range of antidepressants is now available including the tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), reversible monoamine oxidase-A inhibitors (RIMAs), serotonin selective reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants such as mirtazapine and nefazodone. However, clinicians still face a number of problems when selecting the most appropriate antidepressant for a given patient. TCAs are effective in a wide range of patients, but they do have significant drawbacks in terms of their tolerability and safety in overdose, reflecting actions at sites other than those involved in the antidepressant effect. The development of antidepressants that are more selective in their mode of action such as the SSRIs has begun to address the problem of poor tolerability,[1,2] but some concerns have been expressed as to whether they are as effective as TCAs across the range of depressive disorders. The development of reboxetine, a unique selective norepinephrine reuptake inhibitor (selective NRI), provides a new therapeutic alternative for the treatment of depression.[3]

Comprehensive clinical trials have shown that reboxetine is an effective and well-tolerated antidepressant in the general population as well as being effective in the treatment of the severely depressed patient.[4–6] Improvements in social functioning and in patients' perception of their recovery are additional benefits of reboxetine therapy.[7,8] The role of reboxetine in the treatment of depression is discussed in this review in relation to some of the key issues facing medical practitioners.

LONG-TERM EFFICACY

There is a growing recognition of the need for long-term treatment of depression. Even when a patient experiences control of depressive symptoms, there is a 30% to 50% risk of relapse if treatment is discontinued too early.[9] While symptom control may occur in a 6-week period, resolution of the depressive episode may take 4 to 6 months. Therefore, continued therapy is recommended for at least 4 months after a response to therapy is achieved.[10] Prophylactic treatment should also be considered for patients with recurrent depression. This is an important consideration given that 75% to 80% of major depression recurred in a 10-year follow-up study.[11] Furthermore, it seems that patients are protected from recurrence only as long as they remain on antidepressants and that without long-term management depressive episodes are more frequent.[12]

The TCAs amitriptyline and imipramine and the SSRIs sertraline, paroxetine, and citalopram have been shown to be effective when used as continuation therapy to prevent relapse.[9] Imipramine, phenelzine, and the SSRIs fluoxetine, fluvoxamine, paroxetine, and sertraline are effective when used prophylactically. Mirtazapine, venlafaxine, maprotiline, and nefazodone are also effective in long-term treatment. However, not all antidepressants are effective in preventing the recurrence of depression. For example, nortriptyline showed no advantage over placebo in this respect in an elderly depressed population, despite careful plasma level monitoring.[13] To assess the suitability of an antidepressant for prolonged administration, it is essential that efficacy and tolerability are tested in long-term clinical trials. Such clinical trials conducted with TCAs have demonstrated that significant adverse events during treatment often lead to noncompliance, which in turn is thought to lead to relapse and hence an increase in overall care costs.[14,15]

Reboxetine is effective in the acute phase and long-term management of depressed patients as shown in a 1-year, placebo-controlled study.[4] In patients who had previously responded to 6 weeks' treatment with reboxetine, continued therapy with this drug was associated with a significantly lower rate of relapse and recurrence when compared with placebo. Relapse occurred twice as frequently in the placebo group. Reboxetine was also well tolerated over the 1-year study period.[16] There was little difference between the incidence of adverse events in patients receiving reboxetine compared with those receiving placebo. These results demonstrate that

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reboxetine is effective in combined continuation and prophylactic treatment periods and that tolerability is maintained under these conditions.

EFFICACY IN THE ELDERLY

Depression in the elderly is often unrecognized and undertreated despite its relatively high prevalence. Depressive symptoms are frequently reported in the elderly, but major depression is less common than in the younger population. Age alone is not a risk factor for depression, and depression should not be considered a natural consequence of ageing. Depression in older patients differs from that in younger patients in that it is more likely to include sleep and appetite disturbances, somatic complaints, and cognitive dysfunction. The atypical presentation of depression in this age group is further complicated by the frequent existence of comorbid medical conditions that may mask depressive symptoms. In addition to the adverse impact of depression on the patients' quality of life, this condition can lead to increased care costs that reflect more frequent and lengthy hospital stays and increased morbidity and mortality. Furthermore, the suicide rate is worryingly high among the elderly.

Although antidepressant therapy is thought to be effective in around 65% to 75% of older patients,[17] there have been very few properly conducted placebo-controlled studies in old-age depression, and it is difficult to draw formal conclusions. Adverse events are of major importance when determining the most appropriate therapy in this population.[15] Some SSRIs inhibit the cytochrome P450 system, and this has important implications in terms of drug-drug interaction potential given the high use of concomitant medications in this age group.[18] The cardiovascular, hypotensive, cognitive, and sedative adverse effects associated with TCAs[18,19] are particularly undesirable in the older patient as they may exacerbate, rather than alleviate, some symptoms of depression or other medical conditions and increase the risk of falls.

Recent studies suggest that SSRIs are as effective as TCAs. Fluoxetine has been reported to be effective in the over-60 age group in a placebo-controlled study.[20] Dunbar[21] reported that paroxetine was superior to comparators in the elderly.

The efficacy and tolerability of reboxetine in direct comparison with imipramine have been assessed in a very large study in patients with major depressive disorder who were between 56 and 94 years of age.[4] The overall efficacy of reboxetine was comparable to that of imipramine, but reboxetine was associated with a lower frequency of hypotension and related symptoms (most notably in patients with baseline cardiovascular disorders), serious adverse events, adverse event–associated withdrawals, and treatment-related adverse events.[16]

EFFICACY IN SEVERE DEPRESSION

Severely ill and melancholic patients are among the most difficult to treat and are reported to respond less well to antidepressant therapy in general.[22] There has been concern that newer antidepressants, such as RIMAs and SSRIs, are not as effective as TCAs in severely depressed patients. These concerns have been supported by the results of clinical trials by the Danish Antidepressant Group.[23,24] Some recent studies have suggested that SSRIs, particularly fluoxetine, may not be as effective as TCAs in the treatment of severe melancholic depression[25]; however, other studies have found them to be as effective or in some cases more effective.[26]

A recent large-scale, placebo-controlled study, which directly compared the efficacy and tolerability of reboxetine and imipramine, showed that reboxetine was significantly more effective than imipramine in the treatment of melancholic patients and was at least as effective as imipramine in the treatment of severely ill patients.[4] Furthermore, reboxetine was better tolerated than imipramine. Thus, reboxetine may represent an alternative and effective first-line therapy for severely depressed patients without the concomitant adverse events usually associated with TCAs.

SOCIAL ADAPTATION

Traditionally, assessment of the therapeutic efficacy of antidepressants has involved the use of physician or patient rating scales that measure changes in the symptoms of depression. These clearly have their place in defining the role of new antidepressants, and, with standardized study design, make comparison of new and older treatments feasible. Social functioning of psychiatric patients as an outcome measure has been used since the 1960s when interest in how patients adjusted to living in the community became an issue. Several behavior rating scales were developed and used mainly to assess the social adjustment of patients with schizophrenia and the success or otherwise of psychotherapy.[27]

The Social Adaptation Self-Evaluation Scale (SASS) has been developed specifically to measure differences between treatments for depression in terms of social motivation and behavior. The scale has been validated in a survey of over 4000 individuals and in an additional 549 patients with major depressive disorder in a placebo-controlled and a fluoxetine-controlled clinical trial.

A clear differential effect between reboxetine and fluoxetine was observed in the placebo-controlled study, the results of which support the hypothesis that serotonin is involved in regulating mood, while norepinephrine is involved in sustaining drive.[8] Similar results were obtained in the fluoxetine-controlled study (Data on file, Pharmacia & Upjohn). Reboxetine therefore appears to offer a sig-

nificant advantage over fluoxetine in terms of the patients' perception of the efficacy of their treatment and eventual recovery.

TOLERABILITY

Many TCAs are highly toxic and may be lethal when taken in overdose in as little as 10 times the daily recommended dose or when taken in combination with alcohol or other central nervous system depressants. Cardiotoxicity, orthostatic hypotension, and cognitive and perceptual impairment have all been associated with TCAs[18,19,29] as well as an increased risk of seizures particularly in overdose.[30]

SSRIs have a greatly reduced adverse event profile compared with TCAs, which is mainly due to the greater specificity of their site of action. Furthermore, SSRIs do not possess the cardiotoxic properties of TCAs, making them less dangerous than TCAs in overdose and to patients with preexisting cardiovascular disease.[29] They are also not associated with an increased risk of orthostatic hypertension.[31] Nevertheless, SSRIs have been found to cause mild bradycardia and slowing of the sinus node.

The route of metabolism of antidepressants and their potential for drug interactions are important issues in assessing the safety of these agents. Some of the SSRIs have been reported to inhibit the isoenzymes of the cytochrome P450 system. A number of TCAs and SSRIs are metabolized through the cytochrome P450 system, and this has implications for the administration of concomitant medications also metabolized through this route.

The risk of suicide and the safety of antidepressants in overdose are of major importance in the management of patients with depression. There have been concerns that antidepressants can provoke or worsen suicidal ideation or tendencies. It is important to remember, however, that antidepressants will relieve suicidal ideation and tendencies in the majority of patients and there is no clear evidence from clinical trials or from meta-analyses that any antidepressant significantly increases suicide risk. SSRIs have been found to reduce suicidal thoughts faster than reference antidepressants and to protect against the emergence of suicidal thoughts.[32]

Like the SSRIs, reboxetine is associated with a significantly reduced adverse event profile due to its greater specificity of action. Direct comparisons with imipramine and desipramine show reboxetine to have a reduced adverse event profile and a significant advantage in relation to the development of a number of common adverse events including hypotension and related symptoms, dry mouth, and tremor.[6,33] In comparator trials with fluoxetine, patients receiving reboxetine were less likely to experience agitation/nervousness/anxiety or gastrointestinal events.[16] Furthermore, patients treated with reboxetine were more likely to experience marked efficacy in the absence of side effects compared with imipramine or desipramine,[6] and the adverse events they experienced were more likely to be mild to moderate in severity. Reboxetine has been shown to improve sleep length and quality compared with fluoxetine. Reboxetine is not cardiotoxic, and there is no evidence of changes in vital signs or routinely measured laboratory parameters.[5] In the adult population, the frequency of suicide or attempted suicide with reboxetine was 0.3% compared with 0.6% in the placebo group, 0.5% in fluoxetine-treated patients, and 1.0% in imipramine-treated patients.[16] Reboxetine was also not associated with an increase in seizures.[16] Furthermore, from in vitro studies, reboxetine does not interact significantly with cytochrome P450 isoenzymes.

Preclinical studies have shown that reboxetine possesses a favorable safety margin and is tolerated at doses well in excess of those used therapeutically. Furthermore, reboxetine was well tolerated in clinical trials,[16] and it showed no interaction potential with alcohol in healthy volunteers.[34] These findings suggest that reboxetine is likely to prove safe in overdose.

SUMMARY

A comprehensive series of clinical trials have compared the unique selective NRI reboxetine with placebo and with the TCAs 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. In severely depressed patients, reboxetine was significantly more effective than fluoxetine. Reboxetine also offers significant advantages over fluoxetine in terms of social functioning and has a significantly improved adverse event profile compared with TCAs. In comparison with fluoxetine, reboxetine has a different adverse event profile, but shows advantages in terms of agitation/nervousness/anxiety and gastrointestinal events. Reboxetine is not cardiotoxic, and it is not associated with an increased risk of seizures or of orthostatic hypotension. Overall, reboxetine offers a significant safety advantage over TCAs in the treatment of the depressed population and in subsets of the depressed population in an efficacy comparison with the SSRI fluoxetine.

Drug names: amitriptyline (Elavil and others), desipramine (Norpramin), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), maprotiline (Ludiomil), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), venlafaxine (Effexor).

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