A REVIEW OF THE NEW GENERATION ANTIDEPRESSANTS

SUMMARY

+ **A number of new antidepressants - mirtazapine, reboxetine, venlafaxine and nefazodone - are now available.**

+ **The characteristics of these new drugs vary, in many respects, from each other and may have novel modes of action.**

+ **Until more experience is obtained these agents may be best confined to patients who are intolerant of or have had an inadequate response to TCAs or SSRIs**

INTRODUCTION

Depressive illness is a chronic illness that affects people of all ages. It has a lifetime prevalence of 10-25% for women and 5-12% for men.[1] Clinical features of this illness include depressed mood, changes in sleep patterns, reduction in physical energy, feelings of worthlessness, changes in appetite and anhedonia (i.e. loss of pleasurable experiences).[1] Depressed patients experience more impairment of quality of life than patients with common medical disorders.[2] Increased awareness of this condition has resulted in several developments in recent years, in the management of this complex condition. New additions to the range of treatments available are mirtazapine, reboxetine, venlafaxine and nefazodone.

MIRTAZAPINE (ZISPIN®)

Mirtazapine is the first in a new class of antidepressants called the noradrenergic and selective serotonergic antidepressants (NaSSAs).[3] It is chemically distinct from the TCAs and SSRIs. Mirtazapine's primary mode of action is blockade of alpha$_2$ - receptors on the presynaptic noradrenergic and serotonergic neurones. This results in an increase in noradrenergic and serotonergic neurotransmission. Additional effects include antagonism of 5HT$_2$ and 5HT$_3$ receptors thus potentially alleviating some of the effects of the SSRIs such as impotence, sleep disturbances (5HT$_2$ mediated) and nausea (5HT$_3$).[1,3,4,5] High affinity for histamine H$_1$ receptors has also been reported which may result in sedation.[1]

Mirtazapine is recommended initially at a dose of 15mg at bedtime. The dose should be increased at intervals of no less than 1-2 weeks up to a maximum of 45mg per day.[1,3,6,7] Treatment with an adequate dose should result in a positive response within two to four weeks and therapy should be continued until the patient is completely symptom free for four to six months.[6]

Mirtazapine has generally been well tolerated. Pooled data from clinical trials of 1378 patients, reported somnolence, increased appetite and weight gain as the most common adverse effects.[1,4,7,8] The sedative effects of mirtazapine may prove useful in depressed patients with co-morbid insomnia.[3] Tolerance to somnolence may develop with continued administration.[1] In comparison to amitriptyline (n=466), mirtazapine (n=463) was found to have a lower incidence of anticholinergic effects and a similar

incidence of appetite increases, sedative and weight change effects.[4] There have been several reports of overdose with mirtazapine. Doses of up to 975mg have been ingested which resulted in prolonged sedation. No changes in vital signs, ECG abnormalities or convulsions were reported.[1,4,5,6] There is a lack of information regarding the use of mirtazapine in pregnancy and women of child-bearing potential should employ an adequate method of contraception while taking this medication.[6]

Concurrent use of mirtazapine and alcohol or benzodiazepines may result in additive sedative effects.[6,7] Mirtazapine should not be administered concomitantly with MAOIs or within two weeks of cessation of MAOIs.[6,7]

The role of mirtazapine amongst antidepressants has not yet been established. A comparative study with fluoxetine found superior efficacy and tolerability in favour of mirtazapine, with statistically significant reductions in the Hamilton Depression Rating Scale (HAM-D) scores observed.[9] Mirtazapine 20-60mg daily (n=123) was also compared to amitriptyline 75-225mg daily(n=122), in hospitalized patients most of whom were severely depressed. Both drugs were tolerated to the same degree.[1] Data from the manufacturers report similar efficacy to amitriptyline and the side effects of increased appetite and weight gain are reported as mild and transient.[10]

REBOXETINE (EDRONAX®)

Reboxetine is a selective noradrenaline reuptake inhibitor (NARI).[10] It acts predominantly by increasing the action of noradrenaline in the brain, however it also has some weak anticholinergic effects.[3] Reboxetine is indicated for both the acute and long term maintenance of depressive illness. Limited published information is available on this drug. It has been suggested that like mirtazapine, reboxetine has little in-vitro affinity for serotonin uptake sites or postsynaptic receptors. Therefore the typical side-effects such as nausea, seen with the SSRIs are expected to occur infrequently.[3]

Reboxetine is recommended at an initial dose of 4mg twice daily. After three to four weeks the dose may be increased to 10mg daily if the response is inadequate.[3] The maximum daily dose is 12mg.[11]

Short-term controlled clinical trials revealed that reboxetine is well tolerated. The withdrawal rate due to adverse events was comparable to placebo. SSRI type side effects e.g. nausea were no more common with reboxetine than with placebo.[12] In comparison with imipramine (n=241), reboxetine (n=242) was better tolerated with significantly fewer anticholinergic effects being reported.[12,13] Little information is available on overdose with reboxetine. Five cases of overdose involving the use of reboxetine (up to 112mg) alone or in combination have been reported without serious sequelae.[12] Monitoring of cardiac function and vital signs are recommended in the case of overdose.[11] The use of reboxetine is contra-indicated in pregnancy and lactation.[11]

The exact route of metabolism of reboxetine is not known however it is not thought to involve the cytochrome P450 enzyme system. The concomitant use of MAOIs and other antidepressants should be avoided until further information is available.[11,12]

In major depression, reboxetine may offer a tolerability advantage over TCAs. However, published clinical data is too limited for adequate assessment.[8] Most of the information available is derived from the manufacturers. It has been suggested that reboxetine has equal efficacy to imipramine and desipramine with fewer anticholinergic effects, psychomotor impairment and faster onset of action.[10] In comparison with fluoxetine, no difference was observed in efficacy in the overall population. In more severely depressed patients reboxetine was found to produce a greater reduction on the HAM-D scale than fluoxetine.[14]

VENLAFAXINE (EFEXOR®)

Venlafaxine acts by facilitating neurotransmission in the brain through inhibition of the reuptake of both serotonin and noradrenaline (SNRI).[15,16,17] It is thought to have little affinity for histaminergic, muscarinic and adrenergic receptors.[15,16]

Venlafaxine is administered at a dose of 37.5mg BD. If, after several weeks, further clinical improvement is required the dose may be increased to 75mg BD. The maximum recommended dose is 375mg daily.[19] Dose adjustment is necessary in patients with moderate renal or hepatic impairment with a 50% reduction in dose being recommended in these patients.[19,20] Adverse effects most frequently reported include nausea, headache, insomnia and somnolence.[17] Nausea can be severe, especially during the initiation of therapy and may be minimized by beginning with a low dose and gradually titrating upwards.[21] Dose related elevations in blood pressure have been observed and for patients treated with doses greater than 200mg daily routine blood pressure monitoring is advisable.[15,18,19,20] Withdrawal effects have been observed with venlafaxine. To withdraw the drug in patients taking venlafaxine for more than 1 week, the dose should be reduced gradually over 1 to 2 weeks.[19,20] Company data report no serious sequelae in 14 patients following overdose of up to 6.75g.[23] Generalised convulsions and prolonged QT interval have been reported in one patient who consumed 2.75g.[25] Monitoring of cardiac rhythm and vital signs are recommended in overdose.[19] Venlafaxine is contra-indicated in pregnant women and should be avoided in lactating women due to insufficient safety data.[18,19]

Venlafaxine is rapidly absorbed and metabolised in the liver to its active metabolite, O-desmethylvenlafaxine.[18,19] MAOIs and venlafaxine should not be administered concurrently. Fourteen days should be allowed after stopping a MAOI before beginning venlafaxine, a seven day washout period should be allowed between stopping venlafaxine and commencing a MAOI.[19,22]

Comparative studies with imipramine (n=73) reported similar efficacy in the treatment of acute depression.[23] However with treatment of up to one year more patients discontinued imipramine due to lack of effect and adverse drug reactions.[24,25] An outpatient study comparing venlafaxine (n=70) and fluoxetine (n=75), 75mg daily and 20mg daily respectively, for major depression, found a similar rate of efficacy and tolerability.[24,26]

NEFAZODONE (DUTONIN®)

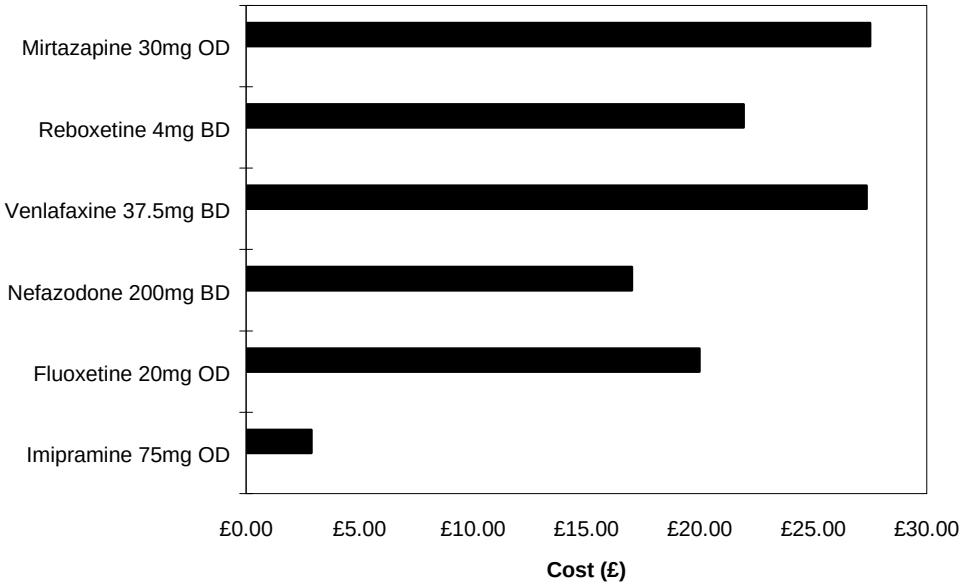
Nefazodone is a phenylpiperazine-derivative antidepressant that is structurally related to trazodone.[18,27,28] Nefazodone exerts its action by inhibition of pre-synaptic reuptake of serotonin, weak inhibition of noradrenaline reuptake and strong antagonism of postsynaptic 5-HT_2 receptors.[18,27]

It is administered at a dose of 100mg twice a day. This dose should be increased to 200mg twice a day after seven days. The maximum recommended dose is 300mg twice a day.[18,29] Based on clinical trials, 16% of patients discontinued therapy due to adverse effects. The most common included dry mouth, somnolence, nausea, dizziness and constipation.[18,27] In comparison to SSRIs, nefazodone has been associated with fewer adverse gastrointestinal effects and fewer adverse effects on sexual function.[27] It has also been reported to improve quality of sleep.[21,24,28] Nefazodone may therefore prove beneficial in the treatment of depression in patients who experience sexual dysfunction or insomnia with other antidepressants.[15] Overdose with nefazodone has been reported rarely. Doses of up to 11.2g have been ingested leading to drowsiness and vomiting. No fatalities have occurred.[27,28,29] As with the other antidepressants discussed previously, little information is available on the use of nefazodone during pregnancy therefore it should only be used if clearly needed.[18,22,29]

Nefazodone is an inhibitor of CYP3A4. Clinically significant drug interactions have been documented with the antihistamines terfenadine and astemizole, resulting in cardiac arrhythmias. Concurrent use should be avoided. The same recommendation applies to concomitant cisapride therapy. Nefazodone therapy should not be initiated until two weeks after discontinuation of a MAOI. When changing to a MAOI from nefazodone a one week washout period should be allowed.[22,24,27,28]

In a study involving 180 patients nefazodone (50-600mg daily) was reported to be as effective as imipramine 50-300mg daily and more effective than placebo.[30] When compared to paroxetine (20-40mg/daily) and sertraline (50-200mg/daily), no differences in efficacy were observed.[31,32]

Cost of 28 Days Therapy (GMS - Nov 98)



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