Treatment of Major Depression: Beyond Generalised Serotonin Potentiation

Increasing recognition of the burden of disability associated with recurrent depression led the authors of a recent article in the *Lancet* to conclude that worldwide, depression produces greater overall health impairment than diseases such as angina, arthritis, asthma and diabetes. Part of the reason for the substantial impact of depression on global health burden is its high life-time prevalence (somewhere between 10-20%). Furthermore, patients with angina, arthritis, asthma and diabetes have a greatly increased risk of experiencing co-morbid depression with correspondingly greater health and social disabilities. Indeed depression itself has been linked to an increased risk of a number of medical conditions such as cardiovascular disease and obesity.

**Treatment of depression**

One of the reasons for the large health burden of depression is that community surveys suggest that only a minority of patients receive effective treatment with psychotherapy and antidepressants. Generic selective serotonin re-uptake inhibitors (SSRIs) such as fluoxetine and citalopram are recommended as first line treatment of moderate depression by the National Institute for Clinical Excellence. However, a recent large investigation in the United States (the STAR*D study) which assessed the response of over 2500 depressed patients to first line treatment with citalopram found that only about one third reached symptomatic remission. In clinical terms, remission means being almost completely free of depressive symptoms and it is an important endpoint because patients who reach this goal show better social and occupation function and have a greater chance of staying well than those with lesser degrees of improvement.

As well as limited efficacy, SSRIs also have a number of adverse effects which limit their acceptability. Early in treatment patients can experience nausea, agitation and insomnia while later problems include sexual dysfunction and persistent sweating. A more recently described problem is an increased risk of gastro-intestinal (GI) bleeding, possibly because SSRIs inhibit the function of blood platelets through lowering platelet serotonin levels. When SSRIs are used as a sole therapy the risk of significant GI bleeding is increased risk of gastro-intestinal (GI) bleeding, possibly because SSRIs inhibit the function of blood platelets through lowering platelet serotonin levels. When SSRIs are used as a sole therapy, the risk of significant GI bleeding is increased risk of gastro-intestinal (GI) bleeding, possibly because SSRIs inhibit the function of blood platelets through lowering platelet serotonin levels. When SSRIs are used as a sole therapy, the risk of significant GI bleeding is increased risk of gastro-intestinal (GI) bleeding, possibly because SSRIs inhibit the function of blood platelets through lowering platelet serotonin levels. When SSRIs are used as a sole therapy, the risk of significant GI bleeding is increased risk of gastro-intestinal (GI) bleeding, possibly because SSRIs inhibit the function of blood platelets through lowering platelet serotonin levels. When SSRIs are used as a sole therapy.

**Pharmacology of SSRIs**

The key pharmacological action of SSRIs is confined to blockade of the re-uptake of serotonin (5-HT) into pre-synaptic 5-HT nerve terminals. This increases the availability of serotonin in the synapse and produces a general activation of all post-synaptic serotonin receptors. Research over the last two decades has shown that serotonin receptors exist in multiple subtypes that have distinct biochemical and functional properties. The identification of these receptor subtypes and the development of selective ligands for them is currently a focus of intense activity in academic and industrial research.

At present researchers have described four main families of 5-HT receptors (5-HT1-A) and some of the families have themselves been subdivided into further receptor subtypes; at present at least 14 pharmacologically distinct 5 HT receptors have been identified. While this is a rapidly developing area, there is already some useful knowledge about the pharmacological correlates of many of these different receptor subtypes and how they may contribute to the therapeutic and adverse effects of antidepressant drugs.

### 5-HT receptors, antidepressant action and adverse effects

The antidepressant effect of SSRIs can be reversed by manipulations such as tryptophan depletion, which lower brain 5-HT synthesis. This indicates that sustained activation of post-synaptic 5-HT receptors is required for the therapeutic effect of SSRIs. However, the specific post-synaptic 5-HT receptors involved in the antidepressant action have not been identified definitively. Post-synaptic 5-HT1A receptors may play a role and selective 5-HT1A agonists such as buspirone and gepirone have antidepressant properties in clinical trials. However, the latter agents do not seem as useful in the treatment of depression as SSRIs because of restricted antidepressant efficacy and relatively poor tolerability. Overall if post-synaptic 5-HT1A receptors do play a role in the antidepressant action of SSRIs, it is likely to be in combination with other 5-HT receptor subtypes.

More progress has been made in understanding the 5-HT receptor subtypes involved in the adverse effects of SSRIs. For example it seems likely that stimulation of 5-HT3 receptors may be involved in the nausea that often accompanies the introduction of SSRI treatment. It is also possible that a number of the adverse effects of SSRIs could be mediated by activation of post-synaptic 5-HT2C receptors. For example, in both humans and animals, the 5-HT2C receptor agonist, m-chlorophenylpiperazine (mCPP), produces anxiety and sleep disruption. As well as reducing sleep continuity, mCPP lowers slow wave sleep, a stage of sleep important for memory consolidation. In contrast, drugs with 5-HT2C receptor blocking properties such as the antidepressant, mirtazapine and the atypical antipsychotic agent, olanzapine, increase slow wave sleep and sleep continuity.

Animal models, acute administration of SSRIs increases anxiety and this effect can blocked by a selective 5-HT2C receptor antagonist.

Taken together these data suggests that the early effects of SSRIs to produce anxiety, agitation and sleep disturbance are probably mediated through activation of 5-HT2C receptors. Another troublesome adverse effect of SSRIs in longer-term treatment is inhibition of ejaculation and orgasm. Animal studies suggest that this effect too may well be mediated in part by activation of 5 HT2C receptors.

### Antidepressants with 5-HT2C receptor blocking properties

The role of 5-HT2C receptors in the adverse effects of SSRIs suggests that combination of 5-HT2C receptor antagonists with SSRIs might be a useful therapeutic strategy from the

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**Table 1: Clinical profile of some commonly used antidepressant medications**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Insomnia</th>
<th>Sedation</th>
<th>Nausea</th>
<th>Weight gain</th>
<th>Sexual dysfunction</th>
<th>Toxicity in Overdose</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>++</td>
<td>0</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>TCA</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

0 = not present, + = sometimes, ++ = common, TCA = Tricyclic Antidepressants and SSRI = Selective Serotonin Reuptake Inhibitors
If found to be expected to be associated with antidepressant effects.

Agomelatine is a recently described molecule which combines melatonin agonist properties with 5-HT2C receptor blockade. Agomelatine is active in animal models of depression and also has proved efficacious in pre-synaptic noradrenergic terminals. This action, rather than 5-HT2C receptor antagonism might therefore account for their antidepressant effects.

There is, however, evidence from basic studies that 5-HT2C receptor antagonism might have antidepressant potential. 5-HT pathways have inhibitory effects on dopamine and noradrenaline release through post-synaptic 5-HT2C receptors. In animal studies blockade of these receptors leads to increased release of both noradrenaline and dopamine, an action which might be expected to be associated with antidepressant effects.

Agomelatine is active in animal models of depression and also has proved efficacious in depressed patients in a number of placebo controlled trials. Interestingly the adverse effect profile of agomelatin does not include early anxiety and insomnia, in fact sleep continuity in depressed patients is improved and slow wave sleep increased. These early data suggest that 5-HT2C receptor antagonists and melanotin agonist are worth exploring as antidepressant agents. If effective such drugs would be expected to have a much lower adverse effect burden than SSRIs and could be particularly helpful for patients troubled by sleep disturbance and sexual dysfunction during SSRI treatment.

References

7. Kahn RS, Wetzler S. Agomelatine is a recently described molecule which combines melatonin agonist properties with 5-HT2C receptor blockade. Agomelatine is active in animal models of depression and also has proved efficacious in depressed patients in a number of placebo controlled trials. Interestingly the adverse effect profile of agomelatin does not include early anxiety and insomnia, in fact sleep continuity in depressed patients is improved and slow wave sleep increased. These early data suggest that 5-HT2C receptor antagonists and melanotin agonist are worth exploring as antidepressant agents. If effective such drugs would be expected to have a much lower adverse effect burden than SSRIs and could be particularly helpful for patients troubled by sleep disturbance and sexual dysfunction during SSRI treatment.

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Please refer to the Summary of Product Characteristics for further information

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Initiation Pack

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In a large study long-term treatment was associated with 2 cases of liver failure. Liver enzyme and full haematological monitoring are recommended at regular intervals (months 1, 3 and 6 on therapy) and periodically thereafter. New or worsening thyroid abnormalities may occur. Thyroid function testing is recommended at baseline and if abnormal every 6 – 12 months. Administer with caution to and monitor closely patients with severe renal and hepatic failure or patients with severe anorexia nervosa. Serum neutralising antibodies against Interferon beta-1a may develop. The clinical significance of these antibodies has not been fully elucidated but is associated with reduced efficacy. If a patient responds poorly and has neutralising antibodies, reassess treatment. Women of childbearing potential should use effective contraception during treatment. 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