

# 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.<sup>1</sup> 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.<sup>2</sup>

## 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.<sup>3</sup> 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 about threefold but in combination with non-steroidal anti-inflammatory drugs (NSAIDs) the risk is much greater (about twelvefold) and prophylaxis with gastro-protective agents has been recommended.<sup>4</sup>

## Pharmacology of SSRIs

The key pharmacological action of SSRIs is confined to blockade of the re-uptake of synaptic 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-HT<sub>1-4</sub>) 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.<sup>5</sup> 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-HT<sub>1A</sub> receptors may play a role and selective 5-HT<sub>1A</sub> agonists such as buspirone and gepirone have antidepressant properties in clinical trials.<sup>6</sup> However, the latter agents do not seem as useful in the treatment of depression as SSRIs because of restricted antidepressant efficacy and relatively poor tolerance. Overall if post-synaptic 5-HT<sub>1A</sub> 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-HT<sub>3</sub> receptors may be involved in the nausea that often accompanies the introduction of SSRI treatment.<sup>6</sup> It is also possible that a number of the adverse effects of SSRIs could be mediated by activation of post-synaptic 5-HT<sub>2C</sub> receptors. For example, in both humans and animals, the 5-HT<sub>2C</sub> receptor agonist, m-chlorophenylpiperazine (mCPP), produces anxiety and sleep disruption.<sup>7</sup> As well as reducing sleep continuity, mCPP lowers slow wave sleep, a stage of sleep important for memory consolidation.<sup>8</sup> In contrast, drugs with 5-HT<sub>2C</sub> receptor blocking properties such as the antidepressant, mirtazapine and the atypical antipsychotic agent, olanzapine, increase slow wave sleep and sleep continuity.<sup>9,10</sup> In animal models, acute administration of SSRIs increases anxiety and this effect can be blocked by a selective 5-HT<sub>2C</sub> receptor antagonist.<sup>11</sup>

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-HT<sub>2C</sub> 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-HT<sub>2C</sub> receptors.<sup>6,12</sup>

## Antidepressants with 5-HT<sub>2C</sub> receptor blocking properties

The role of 5-HT<sub>2C</sub> receptors in the adverse effects of SSRIs suggests that combination of 5-HT<sub>2C</sub> receptor antagonists with SSRIs might be a useful therapeutic strategy from the



**Prof Phil Cowen** is a MRC Clinical Scientist and Honorary Consultant Psychiatrist in the Department of Psychiatry in Oxford. He was elected to a personal Chair in Psychopharmacology at the University of Oxford in 1997 and to a Fellowship in the Academy of Medical Sciences in 2001. His main research interests are in the biochemistry and treatment of mood disorders.

## Correspondence to:

Professor PJ Cowen,  
Neurosciences Building,  
Warneford Hospital,  
Oxford OX3 7JX.  
Email: phil.cowen@psych.ox.ac.uk

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

Drug	Insomnia	Sedation	Nausea	Weight gain	Sexual dysfunction	Toxicity in Overdose
SSRI	++	0	++	+	++	0
Venlafaxine	++	0	++	+	++	+
TCA	0	++	0	++	+	++
Mirtazapine	0	++	0	++	0	0

0 = not present, + = sometimes, ++ = common, TCA = TriCyclic Antidepressants and SSRI = Selective Serotonin Reuptake Inhibitors

point of view of easing the side effect burden of SSRIs therapy. However, might selective 5-HT<sub>2C</sub> receptor antagonists have potential as antidepressants in their own right?

The tetracyclic antidepressants, mianserin and mirtazapine, do not inhibit the re-uptake of noradrenaline or 5-HT but have antagonist properties at 5-HT<sub>2C</sub> receptors. Both these drugs are relatively free from sexual dysfunction and, as noted above, promote sleep. However, they are complex molecules with several other pharmacological actions which makes analysis of the specific effects of 5-HT<sub>2C</sub> blockade difficult to assess. For example, both are strong histamine H<sub>1</sub> receptor antagonists which may well contribute to their ability to improve sleep in depressed patients. H<sub>1</sub> receptor antagonism may also cause the weight gain associated with mianserin and mirtazapine treatment. Mirtazapine and mianserin are also  $\alpha$ <sub>2</sub>-adrenoreceptor antagonists which would be expected to result in increased noradrenaline release from pre-synaptic noradrenergic terminals. This action, rather than 5-HT<sub>2C</sub> receptor antagonism might therefore account for their antidepressant effects.

There is, however, evidence from basic studies that 5-HT<sub>2C</sub> receptor antagonism might have antidepressant potential. 5-HT pathways have inhibitory effects on dopamine and noradrenaline release through post-synaptic 5-HT<sub>2C</sub> 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.<sup>13</sup>

Agomelatine is a recently described molecule which combines melatonin agonist properties with 5-HT<sub>2C</sub> 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.<sup>13,14</sup> Interestingly the adverse effect profile of agomelatine does not include early anxiety and insomnia;<sup>13</sup> in fact sleep continuity in depressed patients is improved and slow wave sleep increased.<sup>15</sup> These early data suggest that 5-HT<sub>2C</sub> receptor antagonists and melatonergic 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

- Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. *Depression, chronic diseases and decrements in health: results from the World Health Surveys*. Lancet. 2007;370:851-8.
- Sherwood Brown E, Varghese FP, McEwan BS. *Association of depression with medical illness: Does cortisol play a role?* Biological Psychiatry. 2004;55:1-9.
- Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. *Evaluation of outcomes with citalopram for depression using measurement-based care in STAR\*D: Implications for clinical practice*. American Journal of Psychiatry. 2006;163:28-40.
- Paton C, Ferrier IN. *SSRI's and gastrointestinal bleeding*. British Medical Journal. 2005;331:529-30.
- Delgado PL, Charney DS, Price LH, Aghajanian GK, Landis H, Heninger GR. *Serotonin function and the mechanism of antidepressant action: Reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan*. Archives of General Psychiatry 1990;47:411-8.
- Stahl SM. *Mechanism of action of serotonin selective reuptake inhibitors*. Journal of Affective Disorders. 1998;51:215-35.
- Kahn RS, Wetzler S. *m-Chlorophenylpiperazine as a probe of serotonin function*. Biological Psychiatry. 1991;30:1139-66.
- Backhaus J, Junghanns K, Born J, Hohaus K, Faasch F, Hohagen E. *Impaired declarative memory consolidation during sleep in patients with primary insomnia: Influence of sleep architecture and nocturnal cortisol release*. Biological Psychiatry. 2006;60:1324-30.
- Sharpley AL, Cowen PJ. *Effect of pharmacologic treatments on the sleep of depressed patients*. Biological Psychiatry. 1995;37:85-98.
- Sharpley AL, Attenburrow ME, Hafizi S, Cowen PJ. *Olanzapine increases slow wave sleep and sleep continuity in SSRI-resistant depressed patients*. Journal of Clinical Psychiatry 2005;66:450-4.
- Burghardt NS, Bush DE, McEwan BS, LeDoux JE. *Acute selective serotonin reuptake inhibitors increase conditioned fear expression: Blockade with a 5-HT<sub>2C</sub> Receptor antagonist*. Biological Psychiatry. 2007 (in press).
- Giuliano F, Clement P. *Physiology of ejaculation: Emphasis on serotonergic control*. European Urology. 2005;48:408-17.
- Stahl SM. *Novel mechanism of antidepressant action: norepinephrine and dopamine disinhibition (NDDI) plus melatonergic agonism*. International Journal of Neuropsychopharmacology. 2007;10:575-8.
- Olie JP, Kasper S. *Efficacy of agomelatine, a MT<sub>1</sub>/MT<sub>2</sub> receptor agonist with 5HT<sub>2C</sub> antagonistic properties in major depressive disorder*. International Journal of Neuropsychopharmacology. 2007;10:661-73.
- Quera-Salva MA, Vanier B, Laredo J, Hartley S, Chapotot F, Moulin C, et al. *Major depressive disorder, sleep EEG and agomelatine: an open-label study*. International journal of Neuropsychopharmacology. 2007;10:691-6.

#### PRESCRIBING INFORMATION - UK AND IRELAND

Please refer to the Summary of Product Characteristics for further information

#### REBIF® 8.8 MICROGRAMS AND 22 MICROGRAMS – SOLUTION FOR INJECTION

Interferon beta-1a

#### Initiation Pack

**Presentation** Each pre-filled glass syringe contains 8.8 or 22 micrograms of Interferon beta-1a in respectively 0.2 or 0.5 ml. **Indication** For the treatment of relapsing multiple sclerosis. Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity. **Dosage and administration** Treatment should be initiated under supervision of a physician experienced in the treatment of multiple sclerosis. For patients initiating treatment with Rebif®, the dosage recommended for the first month of treatment is 8.8 micrograms three times a week by subcutaneous injection for the first two weeks and 22 micrograms three times a week by subcutaneous injection for the following two weeks. From the fifth week Rebif 44 micrograms should be administered. Limited published data suggest that the safety profile in adolescents from 12 to 16 years of age receiving Rebif 22 micrograms by subcutaneous injection three times per week is similar to that seen in adults. Not to be used in patients under 12 years of age. Evaluate patients at least every second year of treatment period. **Contraindications** History of hypersensitivity to natural or recombinant interferon beta, human albumin, or to any of the excipients; initiation of treatment in pregnancy; current severe depression and/or suicidal ideation. **Precautions** Inform patients of the most common adverse reactions. Symptoms tend to be most prominent at the initiation of therapy and decrease in frequency and severity with continued treatment. Use with caution in patients with previous or current depressive disorders and those with antecedents of suicidal ideation. Patients should be advised to report immediately any symptoms of depression and/or suicidal ideation. Patients exhibiting depression should be monitored closely during therapy and treated appropriately. Cessation of therapy should be considered. Administer with caution to patients with a history of seizures and to those receiving treatment with anti-epileptics, particularly if their epilepsy is not adequately controlled. Patients should use an aseptic injection technique and rotate injection sites to minimise risk of injection site necrosis. Patients with cardiac disease should be closely monitored for worsening of their clinical condition during initiation of therapy. Use with caution in patients with history of significant liver disease, active liver disease, alcohol abuse or increased serum ALT. Serum ALT levels should be monitored prior to the start of therapy, at months 1, 3 and 6 on therapy and periodically thereafter. Stop treatment if icterus or other clinical symptoms of liver dysfunction appear. Treatment has a potential to cause severe liver injury including acute hepatic failure. Laboratory abnormalities are associated with the use of interferons. 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 myelosuppression. 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. **Side effects** The majority of adverse reactions observed with Interferon beta-1a are usually mild and reversible, and respond well to dose reductions. In case of severe or persistent undesirable effects, the dose of Rebif® may be temporarily lowered or interrupted, at the discretion of the physician. Very common adverse drug reactions (ADRs) are injection site inflammation/reaction, influenza like symptoms, headache, asymptomatic transaminase increase, neutropenia, lymphopenia, leucopenia, thrombocytopenia, anaemia. Common ADRs are injection site pain, myalgia, arthralgia, fatigue, rigors, fever, pruritus, rash, erythematous or maculo-papular rash, diarrhoea, vomiting, nausea, depression and insomnia. Serious AEs are injection site necrosis, hepatitis with or without icterus, severe liver damage, anaphylactic reactions, angioedema, erythema multiforme, erythema multiforme-like skin reactions, seizures, thromboembolic events, suicide attempt. Consult the Summary of Product Characteristics for more information relating to side effects. Additional information is available on request. **Pharmaceutical precautions** Store in a refrigerator at 2°C to 8°C in the original package. Do not freeze. **Legal category** POM **Basic NHS price** Rebif® Initiation Pack containing: Rebif® 8.8 micrograms - solution for injections: 6 pre-filled syringes (0.2 ml) Rebif® 22 micrograms – solution for injections: 6 pre-filled syringes (0.5 ml) £586.19 Prices in Ireland may differ, consult distributors Allphar Services Ltd **Marketing Authorisation Numbers:** EU/1/98/063/007 **Name and Address of Marketing Authorisation Holder** Sero Europe Ltd, 56 Marsh Wall, LONDON E14 9TP **Name and Address of Distributor in UK** Sero Ltd, Bedford Cross, Stanwell Road, Feltham, Middlesex TW14 8NX **Name and Address of Distributor in Ireland** Allphar Services Ltd, Pharmaceutical Agents and Distributors Belgard Road, Tallaght, Dublin 24, Ireland

**Date of Preparation:** May 2007

**Job Bag:** REB07-0074

Information about adverse event reporting in the UK can be found at [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk). In the Republic of Ireland information can be found at [www.imb.ie](http://www.imb.ie). Adverse events should also be reported to Sero Limited - Tel: +44 (0)20 8818 7373 or email: [medinfo.uk@serono.com](mailto:medinfo.uk@serono.com)

**Date of Preparation:** July 2007

**Job Bag:** REB07-0108

 **serono**  
biotech & beyond