Antidepressants: will new mechanisms of action improve poor outcomes?

Depression is one of the most common mental illnesses and has a high impact on individuals and society. Despite the numerous treatment approaches, poor response combined with the burden of residual symptoms negatively affects the overall outcome. Novel pharmacological approaches could help to address this issue.

Depressive illnesses cause enormous economic burden and disability (Sobocki et al, 2006). Since the serendipitous discovery of the first antidepressants in the 1950s (Bloch et al, 1954) various antidepressants and psychotherapies are recommended in treatment guidelines (McAllister-Williams, 2006). The advent of the selective serotonin-reuptake inhibitors (SSRI) with improved tolerability and safety (Vaswani et al, 2003) has contributed to a 253% rise in antidepressant prescription over the last decade (Moncrieff and Kirsch, 2005). Despite this, there are serious shortcomings in outcomes for patients (Corcoran and McAllister-Williams, 2007). In particular:

1. A significant proportion of depressed patients do not respond to available treatment strategies
2. Among those who respond many experience significant residual symptoms like anxiety, poor sleep, fatigue and pain that negatively impact on the functional outcome (Corcoran and McAllister-Williams, 2007).

In this context it is important to understand that depression is probably a heterogeneous disease, perhaps best viewed as the final expression of various aetiopathogenetic dysfunctions. The clinical presentation of depression is varied and clustering of symptom subsets differs among individual patients. These issues highlight the need for new pharmacological strategies that not only target residual symptoms of depression in various subgroups of depressed patients but also are better tolerated and potentially improve compliance. This article reviews a number of future directions in the pharmacological management of depression, including options that are currently applicable, ones that are due to be available within the next 12–18 months and other promising avenues that may bear fruit in the next 2–10 years.

Novel mechanisms acting on the monoaminergic system

All current pharmacological treatments for depression are thought to act usually by increasing monoaminergic transmission by (1) inhibition of neuronal reuptake (2) inhibition of enzymatic destruction or (3) increasing release. Are there any alternative methods of manipulating monoaminergic systems? Recent studies have provided some interesting results that are applicable in current practice and some that might point to future strategies.

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Receptor-specific strategies

Monoaminergic systems can also be manipulated by drugs that act at specific monoaminergic receptors. The use of selective agonists have been most extensively studied in relation to 5HT1A receptors (Millan, 2004). One such agent, buspirone, is an established treatment in generalized anxiety and does have antidepressant activity (Blier and Ward, 2003). However, pure 5-HT1A agonists may have limited potency as antidepressants although they may play a role as adjunctive agents (Trivedi et al, 2006).

Drugs with direct 5-HT2 antagonist properties, such as mirtazapine or trazadone, produce a significant shortening of sleep-onset latency, increase total sleep time and lead to improved sleep efficiency. Insomnia is a common disabling residual symptom of depression even in those who respond well to existing antidepressants (Nierenberg et al, 1999). Antidepressants with preferential 5-HT2-blocking properties are therefore potential treatment options for depressed patients with marked insomnia (Thase, 1999) and those with residual symptoms including sleep problems.

Some recent data of notable interest concern atypical antipsychotics (with 5-HT2A antagonist properties). A meta-analysis of adjunctive atypicals (olanzapine, risperidone and quetiapine) use in treatment-resistant depression along with conventional antidepressants revealed significantly improved remission rates (Papakostas et al, 2007). Further, Berman et al (2007) have shown efficacy for adjunctive treatment with the antipsychotic aripiprazole in patients with incomplete response to antidepressants. In addition to being a partial D2 agonist, aripiprazole is also a 5HT2 antagonist. The relative contributions of 5-HT2 and D2 activity with this drug in depression needs further exploration (Rasmussen, 2006).

Agomelatine is a new, soon to be licensed antidepressant that is a 5HT2C antagonist (and a melatonergic agonist). Gamma aminobutyric acid (GABA) interneurons tonically inhibit noradrenergic circuits (from the locus coeruleus) and dopaminergic circuits (from the ventral tegmen-

tum) projecting to the prefrontal cortex. 5HT2C receptor stimulation drives these GABA interneurons. Thus, noradrenaline and dopamine circuits are inhibited by the normal tonic release of serotonin (Stahl, 2007). Agomelatine, through 5HT2C inhibition, therefore may in part act as a noradrenaline and dopamine disinhibitor. Clinical trials have confirmed significant antidepressant efficacy for this agent (Olié and Kasper, 2007) although the relative contribution of melatonergic properties of this drug still remains unknown (see below).

Multiple reuptake inhibition strategies

Blockade of either serotonin or noradrenaline is effective in the treatment of depression and blockade of both together may be more potent than one alone in the more severely ill (McAllister-Williams and Tyrer, 2003; Corcoran and McAllister-Williams, 2007). One potential reason for this is that dual reuptake inhibition could be more beneficial for symptoms unaddressed by individual blockade. For example, pain is a common residual depressive symptom and may account for poor response to SSRIs in some patients (Bair et al, 2003; Corcoran and McAllister-Williams, 2007). Dual reuptake inhibitors (noradrenaline and serotonin) have been studied as agents that may target pain symptoms in depression (Thor et al, 2007). Duloxetine and venlafaxine are current options in this regard.

Dopamine abnormalities have been studied largely in schizophrenia, and somewhat neglected in depression so far. Energy, motivation and experience of pleasure together constitute 'positive affect', the loss of which may be related to dopaminergic deficiency (Nutt, 2006) and may be inadequately addressed by serotonergic antidepressants. Bupropion (available but not currently licensed to treat depression in the UK) is a dopamine reuptake inhibitor that may be effective in restoring positive affect rather than simply treating depressive symptoms (Nutt et al, 2007).

In the future triple reuptake inhibitors (acting on 5-HT, noradrenaline and dopamine uptake sites) may be a fruitful source of study in drug development.

Novel non-monoaminergic targets

One reason for the poor outcome in many patients with depression could be the fact that over the past decades monoamine systems have been the sole target of available antidepressants. The recognition of multiple pathophysiological dysfunctions in depression has prompted researchers, clinicians and industry to explore other possible targets in depression. These approaches look set to deliver new option in the very near future.

Hypothalamic–pituitary–adrenal axis

Depression is well known to be associated with hypercortisolaemia. This may be particularly associated with certain depressive symptoms, for example cognitive impairment (McAllister-Williams et al, 1998). Further overactivity of the hypothalamic–pituitary–adrenal (HPA) axis may contribute to reduced antidepressant action. (Young et al, 2004b). This is supported by animal studies demonstrating that corticosteroid administration decreases the ability of an SSRI to increase cortical serotonin (Gartside et al, 2003). Exciting subsequent data suggest that direct glucocorticoid antagonists may do the opposite and enhance the effects of SSRIs (Johnson et al, 2007). These preclinical observations have been supported by clinical data from a pilot study of a glucocorticoid antagonist (mifepristone) improving cognition in bipolar depression (Young et al, 2004a). Further a small clinical trial has shown metyrapone, an inhibitor of glucocorticoid synthesis, to be an effective antidepressant adjunct in unipolar depression (Jahn et al, 2004). Further studies are being conducted exploring this potential avenue and hopefully will bear fruit within the next few years.

Circadian rhythms

Dysregulation of circadian rhythm in depression is evident from the symptoms of diurnal mood change, sleep disturbances and early morning awakening. Further, affective state can be modulated by exposure to environmental light or darkness and sleep deprivation (Wirz-Justice, 2005). Pharmacological manipulation of circadian rhythm may also be possible via melatonergic systems. Agomelatine is an agonist at melatonin (MT1 and MT2) receptors and has been shown to improve the disturbed sleep architecture in patients with depression, addressing a major residual symptom that may prevent full remission (Salva et al, 2007). At present the relative contribution of melatonergic compared to serotonergic action (see above) in agomelatine's antidepressant activity is unclear. However, melatonin itself does not have clear antidepressant activity (Srinivasan et al, 2006).

Neurogenesis

One of the most influential pathophysiological mechanism proposed since the monoamine hypothesis of depression has been HPA axis overactivity (see above) with related neurotrophic changes. It is proposed that depression leads to reduced neurogenesis and that the ultimate effect of antidepressants needs to be increased levels of brain growth factors especially in the hippocampus (Santarelli et al, 2003). It has been shown that directly enhancing neuronal plasticity is a potential novel mechanism in the treatment of refractory depression in pre-clinical studies. Promising future avenues in this regard include the use of N-methyl-D-aspartate antagonists, alpha-amino-3-hydroxy-5-methylisoxazole propionate (AMPA) potentiators, cyclic adenosine monophosphate (cAMP) phosphodiesterase inhibitors, and the bcl-2 family of proteins (Manji et al, 2003). While none of these have been tested in major clinical trials to date, the approach seems rational and may deliver in the future. Meanwhile, indirectly enhancing neuronal plasticity via HPA axis inhibition and glucocorticoid antagonism (see above) may be a viable option in the near future.

Conclusions

Increasing recognition of the inadequacies of existing treatment strategies has stimulated interest in novel drug use and discovery for the management of depression. Some of these efforts may become a part of everyday clinical practice in the near future, but whether this will provide answers to the multiple complex aetio-pathologies seen in depression remains speculative. Moving from a 'one illness – one drug' approach is essential. Such a change may prove too simplistic but remains to be tested. More specific and focussed treatments might actually lead to a better response in subpopulations, but if they are applied without targeting appropriate patients, a less favourable overall outcome in the total population of depressed subjects could result (Buller and Legrand, 2001). Conversely, identification of such subpopulations is important in improving our understanding of the disease and allowing development of more specific and effective treatment strategies. **BJHM**

Conflict of interest: Dr McAllister-Williams has received support to attend academic meetings, honorarium for speaking engagements and attendance at advisory boards, and independent investigator research grant support from a number of pharmaceutical companies who manufacture antidepressants including Eli Lilly, GlaxoSmithKline, Lundbeck, Organon, Pfizer, Servier and Wyeth. Dr Palaniyappan and Dr McAllister-Williams do not hold stock in any pharmaceutical company.

Bair MJ, Robinson RL, Katon W, Kroenke K (2003) Depression and pain comorbidity: a literature review. *Arch Intern Med* **163:** 2433–45

Berman RM, Marcus RN, Swanink R, McQuade RD, Carson WH, Corey-Lisle PK, Khan A (2007) The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* **68:** 843–53

Blier P, Ward NM (2003) Is there a role for 5-HT1A agonists in the treatment of depression? *Biol Psychiatry* **53:** 193–203

Bloch R, Dooneief A, Buchberg A, Spellman S (1954) The clinical effects of isoniazid and iproniazid in the treatment of pulmonary tuberculosis. *Ann Intern Med* **40:** 881–900

Buller R, Legrand V (2001) Novel treatments for anxiety and depression: hurdles in bringing them to the market. *Drug Discov Today* **6:** 1220–30

Corcoran C, McAllister-Williams RH (2007) Maximizing treatment outcomes in the depressed patient. *Br J Hosp Med* **68**: 373–5

Gartside SE, Leitch MM, Young AH (2003) Altered glucocorticoid rhythm attenuates the ability of a chronic SSRI to elevate forebrain 5-HT: implications for the treatment of depression. *Neuropsychopharmacology* **28:** 1572–8

Jahn H, Schick M, Kiefer F, Kellner M, Yassouridis A, Wiedemann K (2004) Metyrapone as additive treatment in major depression: a double-blind and placebo-controlled trial. *Arch Gen Psychiatry* **61:** 1235–44

KEY POINTS

- Depression is a serious illness with significant numbers of patients being refractory to treatment or suffering residual symptoms with only a partial response to treatment.
- Novel therapeutic strategies aimed at various pharmacological targets in the pathophysiological processes of depression are being explored.
- These include the use of more specific monoamine ligands, targetting dopamine in addition to noradrenaline and serotonin, or targetting non-monoaminergic mechanisms such as the hypothalamic–pituitary–adrenal axis or circadian rhythms.
- Some of these novel strategies may well become a part of common clinical practice in the near future.

Johnson DA, Grant EJ, Ingram CD, Gartside SE (2007) Glucocorticoid receptor antagonists hasten and augment neurochemical responses to a selective serotonin reuptake inhibitor antidepressant. *Biol Psychiatry* **62**: 1228–35

Manji HK, Quiroz JA, Sporn J et al (2003) Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. *Biol Psychiatry* **53:** 707–42

McAllister-Williams R (2006) NICE guidelines for the management of depression. *Br J Hosp Med* **67:** 60–1

McAllister-Williams RH, Tyrer SP (2003) Antidepressants for the treatment of depression and anxiety disorders: The same mechanism of action? In: Kasper S, Den Boer JA, Sitsen JMA, eds. *Handbook of Depression and Anxiety: A Biological Approach.* 2nd edn. Marcel Dekker, New York: 443–56

McAllister-Williams RH, Ferrier IN, Young AH (1998) Mood and neuropsychological function in depression: the role of corticosteroids and serotonin. *Psychol Med* **28:** 573–84

Millan MJ (2004) The role of monoamines in the actions of established and "novel" antidepressant agents: a critical review. *Eur J Pharmacol* **500:** 371–84

Moncrieff J, Kirsch I (2005) Efficacy of antidepressants in adults. *BMJ* **331:** 155–7

Nierenberg AA, Keefe BR, Leslie VC et al (1999) Residual symptoms in depressed patients who respond acutely to fluoxetine. *J Clin Psychiatry* **60:** 221–5

Nutt DJ (2006) The role of dopamine and norepinephrine in depression and antidepressant treatment. *J Clin Psychiatry* **67**(Suppl 6): 3–8

Nutt D, Demyttenaere K, Janka Z et al (2007) The other face of depression, reduced positive affect: the role of catecholamines in causation and cure. *J Psychopharmacol* **21:** 461–71

Olié JP, Kasper S (2007) Efficacy of agomelatine, a MT1/MT2 receptor agonist with 5-HT2C antagonistic properties, in major depressive disorder. *Int J Neuropsychopharmacol* **10:** 661–73

Papakostas GI, Shelton RC, Smith J, Fava M (2007) Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. *J Clin Psychiatry* **68:** 826–31

Rasmussen K (2006) Creating more effective antidepressants: clues from the clinic. *Drug Discovery Today* **11:** 623–31

Salva MAQ, Vanier B, Laredo J et al (2007) Major depressive disorder, sleep EEG and agomelatine: an open-label study. *Int J Neuropsychopharmacol* **10:** 691–6

Santarelli L, Saxe M, Gross C et al (2003) Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* **301:** 805–9

Sobocki P, Jonsson B, Angst J, Rehnberg C (2006) Cost of depression in Europe. *J Ment Health Policy Econ* **9:** 87–98

Srinivasan V, Smits M, Spence W et al (2006) Melatonin in mood disorders. *World J Biol Psychiatry* **7:** 138–51

Stahl SM (2007) Novel mechanism of antidepressant action: norepinephrine and dopamine disinhibition (NDDI) plus melatonergic agonism. *Int J Neuropsychopharmacol* **10:** 575–8

Thase ME (1999) Antidepressant treatment of the depressed patient with insomnia. *J Clin Psychiatry* **60**(Suppl 17): 28–31; discussion 46–8

Thor KB, Kirby M, Viktrup L (2007) Serotonin and noradrenaline involvement in urinary incontinence, depression and pain: scientific basis for overlapping clinical efficacy from a single drug, duloxetine. *Int J Clin Pract* **61:** 1349–55

Trivedi MH, Fava M, Wisniewski SR et al (2006) Medication augmentation after the failure of SSRIs for depression. *N Engl J Med* **354:** 1243–52

Vaswani M, Linda FK, Ramesh S (2003) Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review. *Prog Neuropsychopharmacol Biol Psychiatry* **27:** 85–102

Wirz-Justice A (2005) Chronobiological strategies for unmet needs in the treatment of depression. *Medicographia* **27:** 223–7

Young AH, Gallagher P, Watson S, Del-Estal D, Owen BM, Ferrier IN (2004a) Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. *Neuropsychopharmacology* **29:** 1538–45

Young EA, Altemus M, Lopez JF, Kocsis JH, Schatzberg AF, Debattista C, Zubieta JK (2004b) HPA axis activation in major depression and response to fluoxetine: a pilot study. *Psychoneuroendocrinology* **29:** 1198–204