Emerging treatments for major depression

Trevor R Norman and Graham D Burrows[†]

Antidepressant drugs were introduced into clinical practice in the mid-20th Century. While for the most part they have proven effective for the amelioration of depressive symptoms, they are associated with significant deficiencies. These well-recognized shortcomings have given impetus to the pursuit of new molecules that seek to improve on the efficacy, tolerability and safety of existing medications. The following article reviews several new compounds that may have antidepressant potential. Some are more advanced in development, having undergone clinical trials, whereas the clinical potential of others is yet to be explored. For this latter group of compounds, the antidepressant potential relies on their activity in validated animal models. Agomelatine and duloxetine are in the first category, having shown antidepressant efficacy in clinical trials. The blockade of cortisol secretion continues to be a focus of attention for the development of new antidepressants. Thus, synthesis inhibitors, nonpeptide antagonists of corticotropin-releasing factor and glucocorticoid receptor antagonists show some promise in clinical and preclinical tests. Antagonists of the neuropeptide substance P, vasopressin and neuropeptide Y represent a departure of approach from traditional monoamine receptor-based mechanisms. While the clinical results with one substance P antagonist have led to the cessation of further trials, other molecules are in development. Approaches to treatment based on glutamatergic transmission arose from observations in animal models. The clinical evaluation of such compounds awaits further development. The extent to which new agents can be judged to have met the goals of efficacy, tolerability and safety rely not only acute treatment trials but also on longer-term outcomes and postmarketing surveillance. Whether any of the new agents canvassed here prove to be significantly better than existing agents is clearly a judgement for the future.

Expert Rev. Neurotherapeutics 7(2), 203–213 (2007)

CONTENTS

Antidepressant drugs remain one of the main, if not the principal, form of treatment for major depressive disorder. While there are a plethora of medications available for this task, current drugs have many shortcomings, which have been well documented [1]. In response to these deficiencies there is an ongoing search for new agents to overcome them. This search, in part, has been guided by drug design based on existing agents and their putative mechanism of action. This has been less than fruitful in addressing inadequacies of existing medications, since it has not necessarily produced original compounds in terms of putative pharmacological mechanisms. Recent insights from molecular biological approaches to the mechanism of action of antidepressants, holds promise for the discovery of novel treatment paradigms. In particular, the apparent pivotal role of hippocampal neurogenesis in the mechanism of action of the current group of antidepressant agents, has opened the way to new therapeutic targets for the treatment of depression [2]. At present, no new agents based on such a putative mechanism of action have been developed for clinical trials. Conversely, several new compounds that fit within the currently accepted hypotheses regarding antidepressant mechanism of action are currently available in some parts of

[†]*Author for correspondence*
University of Melbourne,
Department of Psychiatry,
Austin Hospital,
Heidelberg 3084,
Victoria, Australia
Tel.: +61 3 9496 5665
Fax: +61 3 9496 3976
graham.burrows@austin.org.au

KEYWORDS:
agomelatine, cortisol, duloxetine, glucocorticoid receptor, glutamatergic receptor, HPA axis, neuropeptide, neurotropic hypothesis, substance P

10.1586/14737175.7.2.203

ISSN 1473-7175

the world. The present paper reviews some of these recently marketed agents and others that are in the early phases of development. The latter agents are only briefly mentioned since, for the majority, their availability for general use is likely to be some time in the future. Clearly, the place of these agents in the treatment of depression is dependent on issues such as short- and long-term safety and efficacy.

Although significantly modified over the years, the monoamine hypothesis of depression and antidepressant drug action still remains an important driving force behind the development of new compounds. Thus, duloxetine has been developed as a dual reuptake inhibitor of the monoamines 5-hydroxytryptamine (serotonin, 5HT) and noradrenaline (NE). Agomelatine is a compound with major effects on the circadian system as well as effects on subtypes of the 5HT receptor system. These two compounds are reviewed in some detail since both are marketed agents (in some countries) and would appear to be closest to more general release worldwide. Compounds based on other strategies such as modification of the Hypothalamic–pituitary–adrenal axis (HPA) or substance-P antagonism have promised a paradigm shift in the treatment of depression. However, their therapeutic potential has not been realized, in that there are no approved treatments based on this foundation. Such compounds continue to be developed starting from a sound theoretical rationale and promising preclinical data. Some representative examples from these classes are also reviewed.

Treatments based on neurotransmitters

Duloxetine

Duloxetine is [(+)-(*S*)-*N*-methyl-γ-(1-naphthalenyloxy)-2-thiophenepropanamine] inhibits 5HT and NE reuptake with equal potency both *in vivo* and *in vitro* [3,4]. The drug has a high affinity for human cloned 5HT and NE transporters *in vitro* and is more potent than venlafaxine [5]. Duloxetine had low affinity for a range of 5HT, muscarinic, adrenergic and histaminergic receptors and did not significantly inhibit monoamine oxidase (MAO) A or B activity [5]. Microdialysis studies of acute doses showed that duloxetine significantly enhanced the release of extracellular levels of both 5HT and NE in the prefrontal cortex and hypothalamus of drug-naïve rats [6]. Conversely, an *in vitro* study in healthy volunteers is at odds with the animal data and suggests that at doses of 20 and 60 mg/day duloxetine was selective for 5HT reuptake inhibition [7]. At higher doses (80 and 120 mg/day), an effect on NE reuptake was evident [8]. The pharmacology of duloxetine implies that it is the effect on both 5HT and NE reuptake that may account for the antidepressant activity of the drug.

The efficacy of duloxetine in the treatment of major depression was first suggested in an open evaluation [9]. Patients received 20 mg of duloxetine once daily for 6 weeks and efficacy was evaluated with the Hamilton Depression Rating (HAM-D) scale. Response based on a 50% or more reduction in the baseline depression score was achieved by 78.2% of subjects, while remission (final HAMD score <6) was achieved by 60.3% of patients. The main side effects of the drug were nausea, insomnia, headache and diarrhoea.

Subsequently, a number of double-blind, placebo-controlled clinical trials of the efficacy of duloxetine in the treatment of depression have been conducted and are summarized in TABLE 1. In these studies, duloxetine was demonstrated to have efficacy superior to that of placebo in trials of 8–9 weeks duration [10–15]. In some studies, a comparative agent was included in the study and duloxetine was at least as effective as fluoxetine [10] or paroxetine [13,14]. In the first of these studies, fluoxetine did not separate from the placebo at any time during the study, although there was an improvement in depression rating scores for the patients treated with this drug. Since relatively few patients were treated with fluoxetine, it is possible that there was insufficient statistical power to show a difference from placebo. In all of these studies duloxetine appeared to be similar to other antidepressants in terms of the number of patients responsive to the medication. There is to date no indication as to the rate of onset of action of duloxetine, although it would appear that the compound is associated with the usual delay of onset with other agents.

In an open-label trial, the efficacy of long-term treatment with duloxetine was assessed in patients with Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV major depressive disorder [16]. In this multicenter study, patients received 40–60 mg of duloxetine twice daily for up to 52 weeks. Efficacy was assessed using the Clinical Global Impression-Severity (CGI-S) scale, the HAM-D and the Beck Depression Inventory (BDI) at baseline, weeks 6, 28 and 52 of treatment. A total of 1279 patients were enrolled in the trial, of whom 553 completed the 52 weeks of therapy. Mean changes from baseline in all efficacy measures were highly statistically significant ($p < 0.001$), using a mixed models repeated measures analysis of variance. The main side effects of treatment were nausea, somnolence, insomnia and headache, which accords with the profile of side effects from the shorter-term studies. The drug appeared to be safe and reasonably well tolerated with no unexpected major adverse events.

The safety and tolerability of duloxetine were addressed in a pooled analysis from eight placebo-controlled comparisons [17]. The database represented 1139 patients treated with doses of duloxetine ranging from 40 to 120 mg/day for up to 34 weeks. Nausea, dry mouth, constipation, insomnia, dizziness and fatigue were the main side effects reported in these studies and all occurred significantly more frequently than with placebo. Cardiovascular assessments showed a slight increase in systolic and diastolic blood pressure as well as heart rate compared with placebo, but were unlikely to be clinically significant. Mean change in the QRS width of the electrocardiogram was also judged not likely to be of clinical significance. The incidence of abnormal laboratory parameters was generally similar between placebo- and duloxetine-treated patients. Most notably, there were increases in liver

Table 1. Clinical trials of duloxetine in treatment of major depressive disorder.

Subjects	Dose	Duration	Outcome	Ref.
70 Dulox 33 Fluox 70 PBO	Up to 60 mg twice daily Fluox 20 mg/day	8 weeks	Dulox > PBO	[10]
123 Dulox 122 PBO	60 mg/day	9 weeks	Dulox > PBO	[11]
128 Dulox 139 PBO	60 mg/day	9 weeks	Dulox > PBO	[12]
86 Dulox 40 91 Dulox 80 87 Parox 89 PBO	20 mg twice daily 40 mg twice daily Parox 20 mg/day	8 weeks	Dulox 40, 80 > PBO Parox = PBO	[13]
95 Dulox 80 83 Dulox 120 86 Parox 69 PBO	40 mg twice daily 60 mg twice daily Parox 20 mg/day	8 weeks	Dulox 80, 120, Parox 20 > PBO	[14]
165 F Dulox 182 F PBO	60 mg/day	9 weeks	Dulox > PBO Weeks 2–9	[15]

Dulox: Duloxetine; F: Female; Fluox: Fluoxetine; Parox: Paroxetine; PBO: Placebo.

enzyme values in patients treated with duloxetine, but the changes were not regarded as clinically important. There was no evidence of a severe withdrawal syndrome following abrupt discontinuation, but it was recommended that the drug be tapered on withdrawal from treatment. There were three deaths in duloxetine-treated patients: one due to suicide, one due to cardiorespiratory arrest and the other to noncardiogenic pulmonary edema.

Agomelatine

Agomelatine (*N*-[2-(7-methoxy-1-naphthyl)ethyl] acetamide) is a naphthalenic bioisostere of melatonin [18]. The compound has been shown to exhibit potent agonist effects at melatonin (MT1 and MT2) receptor sites [18–20]. There was a high affinity for cloned human MT1 and MT2 receptor subtypes comparable to that of melatonin itself [19,20]. On this basis, it could be expected that agomelatine would demonstrate chronobiotic activity. In an experimental animal model of delayed-phase sleep syndrome, agomelatine was capable of resynchronising circadian rhythms [21,22].

Furthermore, it has been shown that agomelatine possesses antagonist properties at $5HT_{2C}$ receptors both *in vivo* and *in vitro* [23,24]. In pig choroid plexus, agomelatine demonstrated a moderately high affinity for $5HT_{2C}$ receptor sites defined by the binding of [3H]-mesulergine [23]. In addition, the drug inhibited the production of inositol phosphate by pig choroid plexus cells, a $5HT_{2C}$ mediated response [23]. Furthermore, there was a dose-dependent inhibition of the penile erectile response induced by the $5HT_{2C}$ agonists, *meta*-chlorophenylpiperazine (mCPP) and Ro-60–0175, in Wistar rats [23]. At cloned human $5HT_{2C}$ receptors, agomelatine acts as an antagonist [24]. As a consequence of this effect, agomelatine dose-dependently increased NE and dopamine concentrations in the frontal cortex of freely moving rats [24]. The effects on neurotransmitters could not be blocked by the selective melatonin antagonist S22153 [24].

In preclinical studies, agomelatine has been shown to be active in tests indicative of antidepressant activity. For example, in the forced swim test agomelatine increased mobility time following acute or repeated doses [25]. This effect was attributed to its $5HT_{2C}$ antagonist properties, as melatonin was inactive in the same test. In the rat chronic mild-stress model of depression, agomelatine 10 and 50 mg/kg has been shown to dose-dependently restore sucrose preference impaired by the stress procedure [26]. In this study, agomelatine was as active as imipramine or fluoxetine. Agomelatine also demonstrated anxiolytic activity in two preclinical models widely used as predictive tests of clinical activity: the Vogel conflict and social interaction tests [27]. The latter property was attributed to the action of the compound as a $5HT_{2C}$ antagonist and not to its effects at melatonin receptors. Thus, agomelatine may represent a novel approach to the treatment of depression, via its chronobiotic activity combined with $5HT_{2C}$ antagonism. On the basis of these animal model studies, agomelatine was selected for further development in the clinic.

Clinical trials have confirmed the antidepressant effect of agomelatine in man [28–30]. Two doses of agomelatine (5 and 100 mg/day) were compared in a double-blind, randomized study in patients with major depressive disorder [28]. Patients had a minimum score on the Montgomery–Asberg Depression Rating Scale (MADRS) of 25 for inclusion after a 1-week placebo run-in period. They were treated for 4–8 weeks and hospitalized for the first 3 weeks of treatment. There were 14 patients per group and neither group differed from the other

at baseline. A total of 19 patients completed 4 weeks of the study. Total MADRS scores decreased from a mean of 30.7 at baseline to a mean of 14.8 in the 5-mg group, and from 31.6–18.6 in the 100-mg group. There was no statistically significant difference between the 5-mg and 100-mg groups for efficacy or safety, although there was some suggestion that 5 mg was slightly more efficacious and better tolerated.

A randomized, double-blind, placebo-controlled trial comparing fixed doses of agomelatine and placebo was performed in 711 patients over an 8-week period [29]. Patients met DSM-IV criteria for major depressive disorder or bipolar II (depressed) disorder. A minimum severity score of 22 on the HAM-D 17-item scale was required at baseline. In the week prior to baseline, all subjects received a placebo in order to exclude rapid placebo responders. After the placebo run-in phase, all eligible patients were randomly assigned to receive fixed doses of agomelatine (1 mg, 5 mg or 25 mg in the evening), paroxetine (20 mg in the morning) or placebo. Assessments with the HAM-D and CGI scales were performed at baseline and weeks 1, 2, 4, 6 and 8. The MADRS and Hamilton Anxiety Scale (HAM-A) scales were performed at baseline and weeks 4 and 8. Analysis of the HAM-D data using analysis of variance with the last observation carried forward (LOCF) data set showed a statistically significant difference between the three agomelatine doses and placebo ($p < 0.05$). Subsequent *post hoc* analysis showed that only the 25 mg dose was superior to placebo. Based on the HAM-D data, paroxetine was also significantly different from placebo at week 8. Analysis of response to treatment, defined as a 50% reduction in the HAM-D score from baseline, showed significantly more responders to treatment on 1 mg agomelatine (62.5%) and 25 mg agomelatine (61.5%) than to placebo (46.3%). Neither 5 mg agomelatine (51.4%) nor paroxetine (56.3%) separated significantly from placebo. For 30.4% of patients treated with 25 mg agomelatine, remission (i.e., HAM-D score of <7) was achieved, compared with 25.7% on paroxetine and 15.4% on placebo. The differences were statistically significant. The drug was reportedly well tolerated with the main side effects being headache (6–9% of patients treated), nausea (3–7%), rhinitis (1–4%) and somnolence (2–4%). A manic switch was noted in two patients (one on agomelatine 5 mg and one on paroxetine), while one patient took an overdose of 90 mg of agomelatine with alcohol and made an uneventful recovery. The data show that 25 mg of agomelatine is effective in the treatment of major depression, but further studies are necessary to confirm the data.

Polysomnographical studies in depressed patients receiving agomelatine (25 mg/day) for 6 weeks showed the drug improved sleep quality and continuity, and increased the duration of slow-wave sleep without modifying rapid eye movement sleep [31]. Although most antidepressants seem capable of improving sleep architecture and symptoms in depressed patients, they may also produce daytime drowsiness or insomnia. Agomelatine appears to relieve the sleep complaints without residual daytime impairments, probably due to its effects on sleep and circadian systems [32].

The ability of agomelatine to produce a withdrawal syndrome following abrupt discontinuation was examined under double-blind, placebo-controlled conditions [30]. After 12 weeks of treatment with agomelatine 25 mg/day or paroxetine 20 mg/day, sustained remitters were randomly assigned for 2 weeks to placebo or their initial treatment. Discontinuation symptoms were monitored using the Discontinuation Emergent Signs and Symptoms (DESS) checklist. A total of 192 patients were randomized to the 2-week discontinuation period. There were no discontinuation symptoms in patients abruptly ceasing agomelatine, whereas those ceasing paroxetine had an increase in the number of symptoms over those remaining on paroxetine. It was concluded that agomelatine is not associated with a discontinuation syndrome unlike paroxetine, which is well recognized to have this effect.

Dopamine receptor agonists

Dopamine is well known to be involved in the reward system of the brain. Given that anhedonia is a characteristic feature of depression, it is surprising that dopaminergic agents have not received greater prominence in the treatment of the disorder. Both bupropion and nomifensine (which was withdrawn from the market due to hemolytic anemia in some patients), two effective antidepressant agents, have effects on the reuptake of dopamine. Bupropion also has effects on NE reuptake. A potential drawback of drugs that potentiate dopamine transmission is that they are likely to have abuse potential, although this does not appear to be the case with either bupropion or nomifensine. It is not surprising, therefore, to find several dopamine active agents either in clinical trials or in preclinical development.

In preclinical studies, dopamine agonists have been tested for antidepressant and anxiolytic activity. The preferential dopamine D3 agonist 7-OH-DPAT and a partial dopamine agonist, *N*-[4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl]-2-naphthylcarboxamide (BP 897) both demonstrated anxiolytic effects in the elevated plus maze [33]. Only 7-OH-DPAT was shown to be antidepressant in the forced swim test. Conversely, BP 897 potentiated the effects of imipramine in this test. The study highlights a potential role for dopamine D3 agents either as antidepressants in their own right or as augmentation agents.

The utility of dopamine D2/D3 agonists as antidepressants or as augmentation agent has been demonstrated in several clinical trials with pramipexole. Thus in a double-blind, controlled study, three doses of pramipexole (0.375, 1.0 or 5.0 mg) were compared with fluoxetine (20 mg) and placebo [34]. After a placebo run-in week, patients with major depression were randomly allocated to one of the treatments and efficacy evaluated with the HAM-D and MADRS scales. By end point (week 8), both fluoxetine and the 1.0 mg dose of pramipexole had statistically significant improvement over placebo. The 5 mg dose was effective but there was a substantial drop-out rate in this group due to the side effects of vomiting, hypomania, psychomotor agitation, loss of impulse control and ataxia.

A smaller, double-blind, placebo-controlled study was conducted in 21 patients with bipolar II depression who were receiving either lithium or valproate [35]. Patients received the additional medication for 6 weeks and efficacy was evaluated using the MADRS scale. A statistically significant decrease in MADRS score was observed in 60% of patients receiving pramipexole compared with 9% in patients receiving placebo.

In other studies, pramipexole also demonstrated antidepressant efficacy as an augmentation agent. In a review of the charts of 32 patients who received pramipexole 0.70 mg/day for 24 weeks, 50% of patients with unipolar depression and 40% of patients with bipolar depression were rated as improved [36]. In an open evaluation, either pramipexole or ropindole (also a dopamine agonist) were added to ongoing treatment with antidepressants or mood stabilizers in patients with bipolar II depression [37]. The mean final dose of pramipexole was 1.23 mg/day and, of ropindole, 2.97 mg/day. Response was noted in 44.4% of patients while another 27.8% had a transient improvement in this otherwise refractory group. Pramipexole was added to antidepressant treatment with tricyclic antidepressants or SSRIs in patients with treatment-resistant depression [38]. Based on a reduction of 50% or greater of MADRS baseline, 67.7% of patients were responders to pramipexole addition. The mean dose of pramipexole was 0.95 mg/day. The long-term safety of pramipexole addition to tricyclics or specific 5HT reuptake inhibitors was evaluated in 23 patients with treatment-resistant major depression [39]. The mean dose of pramipexole was 0.99 mg/day and the median follow-up was 28 weeks. Overall, 60.9% of patients were responders to the addition of the dopamine agonist.

Together, these data suggest a role for direct-acting dopamine D2/D3 agonists or indirect-acting agonists, such as by dopamine reuptake blockade in the treatment of depression. At present, apart from bupropion, there do not appear to be any individual agents available as antidepressants. Nevertheless, the data with pramipexole would suggest that this agent might be effective if used alone. Certainly, the evidence supports a role for this agent as an adjunct to other antidepressants in cases of treatment failure or resistance. The potential for the precipitation of manic or hypomanic episodes as well as an unknown addiction potential may prove to be an insurmountable hurdle in the development of antidepressants based on this mechanism.

Serotonin noradrenaline reuptake inhibitors

As noted above, the recently marketed duloxetine can be considered an antidepressant in this class. The notion that so-called dual action antidepressants are more efficacious than agents with putative effects on a single neurotransmitter has gained acceptance, following recent meta-analyses of controlled clinical trials [40,41]. At least in cases of severely depressed in-patients, the older tricyclic antidepressants appear slightly more effective than the selective serotonin reuptake inhibitors. Nominally, tricyclic antidepressants affect both 5HT and NE reuptake with variations among the different agents. Given the apparent clinical efficacy of such drugs compared with single-action agents, a strategy for developing dual-action drugs without the tricyclic (anticholinergic) side-effect profile would seem to be inherently beneficial. Furthermore, there is evidence that the dual-acting drugs have beneficial effects in various pain states, such as fibromyalgia syndrome, neuropathic pain, headache and other conditions [42]. Indeed, both venlafaxine and milnacipran marketed because currently antidepressants both block 5HT and NE reuptake [41]. A third agent, mirtazapine, has been described as a dual-acting drug by virtue of indirect effects on serotonergic transmission and enhancing NE release by antagonism of pre-synaptic α_2-adrenoceptors [43]. There are few data to judge whether these agents have superior efficacy to the tricyclic antidepressants in either in-patient populations or those with the melancholic subtype of depression. Some qualitative reviews suggest that they do not [44].

More recently, the benzocyclobutane derivative S33005 has been shown to potently bind to rat and human 5HT and NE transporters [45]. Moreover, the compound elevated extracellular NE and 5HT in the prefrontal cortex of the freely moving rat [45]. In a series of preclinical tests, S33005 demonstrated behavior suggestive of antidepressant activity, most notably in the chronic mild-stress paradigm and the forced-swim test [46]. Furthermore, the effect of the drug on the sleep architecture of rodents was consistent with an antidepressant profile [47].

Neuropeptide modulators

Hypothalamic–pituitary–adrenal axis

The involvement of the HPA axis in depression was first suggested by the observation of raised plasma cortisol in patients [48]. This was subsequently confirmed by Gibbons [49]. Up to 50% of patients with major depression have an associated hypercortisolemia, while in some subtypes of depression the rates may be higher [50,51]. With recovery from depression, hypercortisolemia has been shown to normalize, suggesting that this is a state, rather than a trait marker of the illness [51]. Disturbances of circadian rhythmicity of cortisol and elevated concentrations of corticotropin-releasing factor (CRF) have also been reported more recently [52,53]. Both the hypersecretion of CRF and hypercortisolemia are believed to arise as a consequence of impaired feedback inhibition by endogenous corticosteroids. The hypersecretion of cortisol in depression has been suggested to result in hippocampal volume loss, which, in turn, contributes to the loss of feedback control of glucocorticoid release [54]. Furthermore, the failure of the synthetic glucocorticoid, dexamethasone, to suppress cortisol secretion has been taken to indicate an abnormality of glucocorticoid receptors in depression [54]. Secretion from the hypothalamus of CRF, a 41 amino acid peptide, controls the release of adrenocorticotropic hormone (ACTH), which in turn stimulates the release of cortisol from the adrenal glands [51]. The treatment of depressive illness by the modulation of the activity of the HPA axis and/or CRF, has therefore, provided a target for the development of several agents.

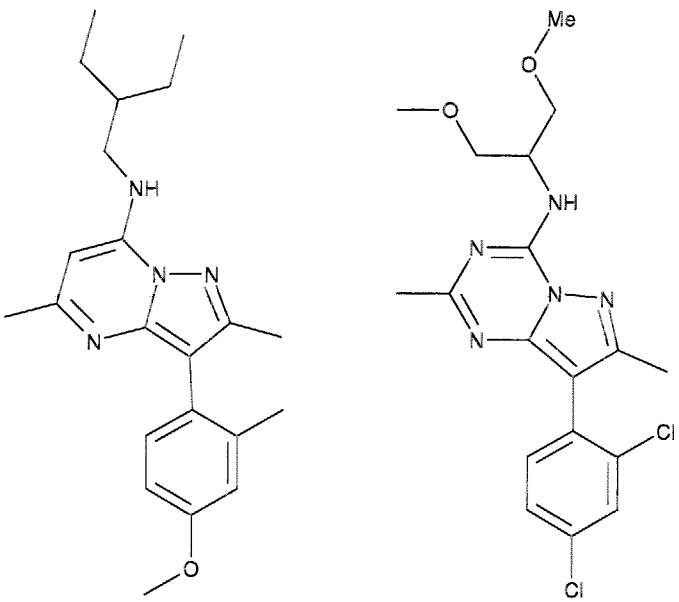

Figure 1. Chemical structure of some nonpeptidergic corticotropin-releasing factor-1 antagonists.

Raised concentrations of cortisol can be diminished by the administration of steroid synthesis inhibitors. Some studies have used the antifungal agent ketoconazole as well as metyrapone or aminogluthemide as treatments for depression based on this strategy. The results from double-blind, placebo-controlled studies have been inconsistent [55,56]. This is a strategy likely to be of limited efficacy since not all patients have elevated plasma cortisol. Furthermore, elevations of cortisol may be secondary to other phenomena, and not causal. Underlining the limitations of this strategy are the results of two double-blind, placebo-controlled evaluations of ketoconazole in major depression. In 20 patients with major depressive disorder Wolkowitz and colleagues showed a significant antidepressant effect of ketoconazole over placebo, but only in those patients with hypercortisolemia at baseline [57]. In a similar patient group, no therapeutic effect of the drug was observed [58].

A more promising approach has been to use the glucocorticoid receptor antagonist mifepristone. Initial clinical studies with this compound have shown efficacy in psychotic depressive episodes [59,60]. Further clinical evaluations of this compound are necessary to appraise its suitability for general marketing approval.

The CRF family of neuropeptides includes not only CRF itself but the more recently identified peptides urocortin, urocortin II and urocortin III [61]. These peptides bind with different affinities to the two major CRF-G-protein coupled receptor subtypes. Many peptide and nonpeptide ligands have been synthesized as modulators of CRF receptor function and several have shown potential antidepressant and anxiolytic properties in animal models [62]. Thus, the CRF1 antagonist, DMP904 (FIGURE 1), was shown to be anxiolytic in the elevated plus maze and defensive withdrawal paradigm in rats [63]. Furthermore, the compound blocked the stress-induced rise in plasma corticosterone. A further CRF1 antagonist, CP-154,526 demonstrated both anxiolytic and antidepressant-like effects in various preclinical models [64,65]. In a 4-week, double-blind study ORG 34517 demonstrated significant antidepressant effects [66]. The efficacy of the potent CRF antagonist R121919 was investigated in 24 patients with major depression [67]. Patients were assigned to treatment with two different dose-escalating regimens: 5–40 mg/day and 40–80 mg/day. Four patients withdrew from the study, leaving 10 completers for the 30-day treatment period in each group. There was a statistically significant decline in HAM-D scores from baseline in both groups, with greater effects observed in the patients treated with the higher dose. There does not appear to have been any further development of this compound. Clinical investigations for others drugs in this class are underway but none of the molecules has been marketed.

Neurokinin-1 (substance P) antagonists

Substance P belongs to a family of neuropeptides known as tachykinins, which share a common C-terminal sequence. Biological effects are mediated through G-protein-coupled receptors. At least three receptor subtypes have been identified and designated neurokinin (NK)1, NK2 and NK3 [68]. Both substance P and its receptors are highly expressed in brain regions critical for the regulation of emotion and stress: the striatum, amygdala, hypothalamus, ventral tegmental area, parabrachial nucleus and locus coeruleus [69]. The effects of antagonists are highly-species dependent, such that NK1 antagonists which have high affinity for guinea pig and gerbil receptors also bind with similar affinity to human receptors [68]. Initial clinical trials with the compound MK-869 (aprepitant) demonstrated it to be more effective than placebo and at least as effective as the selective serotonin reuptake inhibitor (SSRI) paroxetine [70]. In this double-blind trial, 213 patients with major depression were randomly assigned to placebo, paroxetine (20 mg) or MK-869 (300 mg), once daily for 6 weeks. Efficacy was assessed using the HAM-D scale. The number of responders to treatment at

the end of the study was 54% for MK-869, 46% for paroxetine and 28% with placebo, defining responders to treatment as a decline of the HAM-D score from baseline as more than 50%. The results showed a proof of concept for substance P antagonists in the treatment of depression. A dose-finding study was conducted in which patients were assigned to one of four doses of MK-869 (10, 30, 100 or 300 mg/day), fluoxetine 20 mg/day or placebo [71]. The trial was conducted over 6 weeks and employed double-blind methodology. The HAM-D scale was used to evaluate the efficacy of the drug. Improvements after 6 weeks of treatment were similar in all arms of the study. Thus, no conclusions could be drawn from this trial about the antidepressant efficacy of MK-869. A variant of this compound with higher oral bioavailability and greater brain penetration was also tested in clinical trials. While the initial study versus placebo was positive, a dose finding study did not show separation from placebo [71]. Further development of this compound was terminated. Thus, the role of NK1 antagonists as antidepressants remains equivocal. Further compounds have been developed and are in early phase clinical studies.

Vasopressin

The role of vasopressin and its receptors in the treatment of psychiatric disorders was first suggested by the observations of Gold and colleagues, who noted the similarities between the symptoms of depression and the effects of arginine vasopressin (AVP) [72]. Subsequently, correlations between plasma and cerebrospinal fluid concentrations of AVP and depressive symptomatologies were observed [73,74], while antidepressant drugs were found to lower the concentration of AVP [75].

With advances in the understanding of the actions of AVP and the receptor subtypes on which it acts, specific agents have been developed that demonstrate antidepressant properties. At least three subtypes of AVP receptor have been characterized in the CNS [76]. Both the V1 and V3 receptor have been the targets for preclinical evaluation of potential new antidepressant compounds. Thus, the V1 receptor antagonist $D(CH_2)_5Tyr(CH_3)AVP$ is active in the forced-swim test when injected into the septum or amygdala of rats [77,78]. A role for V3 receptor antagonists as antidepressants has been suggested from the demonstration that SSR149415 is active in blocking stress and CRF-induced increases in plasma ACTH [79]. V3 receptor knockout mice exhibit marked reductions in AVP and stress-induced ACTH release [80]. Overactivity of the HPA axis is also a target of antidepressant drug development (*vide supra*) and, therefore, V3 antagonists may be antidepressant via an indirect effect on cortisol secretion. In both the chronic mild-stress paradigm and the forced swim test SSR149415 produces dose-dependent antidepressant-like effects [81,82]. The fact that the effects in the forced swim test were present in hypophysectomised animals suggests that the antidepressant-like effect is independent of the influence over the HPA axis [82]. Clinical evaluations of V1 and V3 receptor antagonists are awaited with interest.

Other compounds

Potential for antidepressant activity in compounds with primary putative mechanisms of action not affecting traditional monoamine targets have been indicated in preclinical models. The ability of chronically administered antidepressant agents from different classes to modulate the activity of the *N*-methyl-D-aspartate (NMDA) receptor has been demonstrated in animal studies [83,84]. Thus, preclinical attention has focused on NMDA receptor antagonists with 2-amino-7-phosphoheptanoic acid (AP-7), 1-aminocyclopropancarboxylic acid (ACPC) and memantine, which have been shown to be active [85]. Similarly, compounds affecting the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor, such as LY392098 and LY451646, have also demonstrated antidepressant effects in animal model studies [86]. The activity of compounds acting at various glutamatergic receptors awaits demonstration in methodologically sound clinical trials.

The modulation of several neuropeptide systems has been implicated in either the etiology of depression or from preclinical models where antidepressant-like activity has been displayed [87]. Alterations in neuropeptide Y (NPY) activity, gene expression and function have been demonstrated in several putative animal models of depression [88]. Similarly, chronic antidepressant treatment has been shown to alter NPY function [88]. The available data suggest that the NPY Y1 receptor subtype is the most likely target for the development of treatment strategies. Possible roles for other NPY receptor subtypes are not known at this time. Antidepressant activity for NPY has been demonstrated in the forced-swim test [89]. Clearly, the development of specific agonists and antagonists to the family of NPY receptors is necessary to further evaluate the potential of this group of receptors to provide clinical therapeutic strategies in the treatment of depression.

Melanin concentrating hormone (MCH) plays an important role in the regulation of energy balance and body weight [90]. The effects of MCH are mediated through G-protein-coupled receptors with two subtypes of receptor identified in humans [91]. The central distribution of the MCH-R1 receptor is suggestive of a role for MCH in mood- and stress-related disorders [92]. The MCH-R1 antagonist SNAP-7491 was tested in the rat forced-swim test and the guinea pig ultrasonic vocalization test. In both tests, there was a dose-dependent antidepressant-like effect of the drug. In the forced-swim test a dose of 30 mg/kg was equivalent to that of 10 mg/kg fluoxetine [92]. At this time, there does not appear to have been any clinical testing of the compound. The data suggest that MCH-R1 antagonists may offer a new therapeutic approach to depression, although weight loss induced by such compounds may be problematic in clinical usage.

Conclusions

Many of the compounds presented in this brief overview of potential antidepressants are unlikely to reach clinical practice. The nature of research in this area is designed to fail compounds that are clearly ineffective or that have associated toxicity issues. It is often the case that substances with promising

preclinical profiles fail to reach the clinic owing to these issues. Recent approaches to the treatment of depression have advanced beyond a simplistic monoamine hypothesis of the disorder. Conversely, much of our approach to treatment still derives from an understanding of the neurochemical effects of existing agents. While the present understanding is more sophisticated than that of 30 years ago, this approach still suffers from the shortcoming of not approaching treatment from a greater understanding of the neurochemical etiology of depression itself. Recent developments in understanding the mechanism of action of antidepressants promise a paradigm shift in thinking about depression and generational changes in treatment. Rather than treatments affecting cell-surface receptors, various signal transduction cascades appear to be an important determinant; not simply of the mechanism of action of conventional drugs, but perhaps the etiology of the illness itself [93]. Thus, modulation of the cyclic AMP (cAMP)-transduction cascade coupled to G-protein receptors and a functional upregulation of cAMP-response element binding protein (CREB) has been shown to be a common effect of antidepressant treatments [94]. Furthermore upregulation of CREB, results in an increased production of the neurotropin brain-derived neurotropic factor, suggesting that activation of this protein may be a novel approach to depression treatment [2]. Indeed, it has been shown in preclinical studies that brain-derived neurotropic factor itself possesses antidepressant-like effects [95,96]. Thus, modulation along crucial signal-transduction pathways may provide a new generation of drugs for the treatment of depression. At present, such approaches are necessarily theoretical, but in the future, may resolve some of the current clinical shortcomings of the present generation of antidepressants.

Expert commentary

Depression remains a significant public health issue and is likely to do so into the future. Treatments for the illness with efficacy in the maximum number of patients, a rapid onset of action and minimal side effects are highly sought after. To date these have proved to be elusive goals, while the current group of medications does not seem to be any better placed than existing compounds to achieve them. It is likely that rapid relief (within 2–3 days of commencing medication) of the symptoms of depression cannot be achieved because of the necessity to re-establish a disturbed homeostatis. While this represents a nihilistic point of view, consideration of the course of changes in receptor function suggests that there is a limit to the rate of receptor (and almost certainly gene and other intracellular) adaptation. What may be more important in the longer-term treatment of depression is that patients achieve a full remission of symptoms, rather than just an improvement. While remission can be achieved with both the existing and the newer compounds described in this review, the time to achieve such an outcome can be protracted. At present, there is no indication of whether any of the potential agents canvassed here can achieve remission earlier than that of any of the existing agents. However, this needs to be a goal of new drug therapies, as relapse occurs frequently in depression, while there is some evidence that achieving full remission may be protective against further relapses. Strategies based on the direct manipulation of neurotropic factors, should they be realized, may offer advantages in this respect. However this remains highly speculative and awaits the results from appropriately designed clinical studies.

Five-year view

Improved medication for the treatment of depression has involved a continuing search based in part on hypotheses of the prevailing knowledge of the mechanism of antidepressant drug action. Clearly, no drug has emerged from this research approach in the past five decades that can be regarded as the ideal antidepressant. Furthermore, response to medication remains highly variable with no *a priori* indicators of responsiveness in individual patients. The next 5 years are likely to bring more of the same: receptor mechanism-based treatments with their efficacy in individuals dependent on trial and error. However, new data on antidepressant mechanisms emerging in the last 5 years or so is likely to provide a more specific hypothesis-driven search for compounds which affect intracellular cascades. This, coupled with the use of pharmacogenetic techniques to match individual patients to particular drug treatments, may well provide the stimulus for the development of future medications in the next 5 years and beyond.

Key issues

- Monoamine neurotransmitter-based drugs (reuptake blockers, receptor antagonists) form the next group of antidepressants to be available for clinical use.
- Strategies for the treatment of depression based on manipulation of dopamine concentrations have been relatively neglected.
- Some promising approaches to symptomatic relief of depression have utilized dopamine agonists as adjunctive therapies.
- Despite considerable effort, corticotropin-releasing factor and substance P antagonists have not yet yielded drugs successful as antidepressants in the clinic.
- Approaches to the treatment of depression with other neurohormone modulators have identified some promising candidate molecules in preclinical tests.
- Hypotheses of antidepressant action based on neurogenesis may provide an avenue for the development of new agents for the treatment of depression.

References

Papers of special note have been highlighted as:
- • of interest
- •• of considerable interest

1 Nemeroff CB, Owens MJ. Treatment of mood disorders. *Nat. Neurosci.* 2(Suppl.), 1068–1070 (2002).

• **Similar but briefer overview of the treatment of depression to that of the current paper with a focus on the neurotropic and hypothalamic–pituitary–adrenal axis hypotheses of depression.**

2 Malberg JE, Schechter LE. Increasing hippocampal neurogenesis: a novel mechanism for antidepressant drugs. *Curr. Pharmaceut. Design* 11, 145–155(2005).

•• **Detailed focus on the evidence for the neurotropic hypothesis of depression reviewing mostly preclinical data.**

3 Wong DT. Duloxetine (LY248686): an inhibitor of serotonin and noradrenaline uptake and an antidepressant drug candidate. *Exp. Opin. Invest. Drugs* 7, 1–9 (1998).

4 Kasamo K, Blier P, de Montigny C. Blockade of serotonin and norepininephrine uptake processes by duloxetine: *in vitro* and *in vivo* studies in the rat brain. *J. Pharm. Exp. Ther.* 277, 278–286 (1996).

5 Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG *et al.* Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters *in vitro* and *in vivo*, human serotonin receptor subtypes and other neuronal receptors. *Neuropharmacol.* 25, 871–880 (2001).

6 Engleman ES, Perry KW, Mayle DA, Wong DT. Simultaneous increases of extracellular monoamines in microdialysates from hypothalamus of conscious rats by duloxetine, a dual serotonin and norepinephrine uptake inhibitor. *Neuropharmacol.* 12, 287–295 (1995).

7 Turcotte JE, Debonnel G, de Montigny C, Herbert C, Blier P. Assessment of the serotonin and norepinephrine reuptake blocking properties of duloxetine in healthy subjects. *Neuropharmacol.* 24, 511–521 (2001).

8 Vincent S, Bieck PR, Garland EM *et al.* Clinical assessment of norepinephrine transporter blockade throughy biochemical and pharmacological profiles. *Circulation* 109, 3202–3207 (2004).

9 Berk M, Du Pleiss AD, Birkett M *et al.* An open label study of duloxetine hydrochloride, a mixed 5-HT and noradrenaline re-uptake inhibitor, in patients with major depressive disorder. *Int. Clin. Psychopharmacol.* 12, 137–140 (1997).

10 Goldstein DJ, Mallinckrodt CH, Lu Y, Demitrack MA. Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. *J. Clin. Psychiat.* 63, 225–231 (2002).

11 Detke MJ, Lu Y, Goldstein DJ, Hayes JR, Demitrack MA. Duloxetine, 60mg once daily for major depressive disorder: a randomized double-blind placebo-controlled trial. *J. Clin. Psychiat.* 63, 308–315 (2002).

12 Detke MJ, Lu Y, Goldstein DJ *et al.* Duloxetine, 60 mg once daily dosing versus placebo in the acute management of major depression. *J. Psychiat. Res.* 36, 383–390 (2002).

13 Goldstein DJ, Lu Y, Detke MJ. Duloxetine in the treatment of depression. A double-blind placebo-controlled comparison with paroxetine. *J. Clin. Psychopharmacol.* 24, 389–399 (2004).

14 Detke MJ, Wiltse CG, Mallinckrodt CH *et al.* Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *Eur. NeuroPsychopharmacol.* 14, 457–470 (2004).

15 Burt V, Wohlreich MM, Mallinckrodt CH *et al.* Duloxetine for the treatment of major depressive disorder in women ages 40 to 55 years. *Psychosomatics* 46, 345–354 (2005).

16 Raskin J, Goldstein DJ, Mallinckrodt CH *et al.* Duloxetine in the long-term treatment of major depressive disorder. *J. Clin. Psychiat.* 64, 1237–1244 (2003).

17 Hudson JI, Wohlreich MM, Kajdasz DK. Safety and tolerability of duloxetine in the treatment of major depressive disorder: analysis of pooled data from eight placebo-controlled clinical trials. *Human Psychopharmacol.* 20, 327–341 (2005).

18 Depreux P, Lesieur D, Mansour HA *et al.* Synthesis and structure–activity relationships of novel naphthalenic and bioisoteric related amidic derivatives as melatonin receptor ligands. *J. Med. Chem.* 37, 3231–3239 (1994).

19 Yous S, Andrieux J, Howell HE *et al.* Novel naphthalenic ligands with high affinity for the melatonin receptor. *J. Med. Chem.* 35, 1484–1486 (1992).

20 Conway S, Canning SJ, Howell E *et al.* Characterization of human melatonin Mt1 and MT2 receptors by CRE-luciferase reporter assay. *Eur. J. Pharmacol.* 390, 15–24 (2000).

21 Redman JR, Guardiola-Lemaitre B, Brown M, Delagrange P, Armstrong SM. Dose-dependent effects of S20098, a melatonin agonist on direction of reentrainment of rat circadian rhythms. *Psychopharmacol* 118, 385–390 (1995).

22 Armstrong SM, McNulty OM, Guardiola-Lemaitre B, Redman JR. Successful use of S20098 and melatonin in an animal model of delayed sleep-phase syndrome. *Pharmacol. Biochem. Behav.* 46, 45–49 (1993).

23 Chagraoui A, Protais P, Filloux T, Mocaer E. Agomelatine (S20098) antagonizes the penile erections induced by the stimulation of 5HT2C receptors in Wistar rats. *Psychopharmacol.* 170, 17–22 (2003).

24 Millan MJ, Gobert A, Lejeune F *et al.* The novel melatonin agonist agomelatine (S20098) is an antagonist at 5-hydroxytryptamine 2C receptors, blockade of which enhances the activity of frontocortical dopaminergic and adrenergic pathways. *J. Pharm. Exp. Ther.* 306, 954–964 (2003).

25 Bourin M, Mocaer E, Porsolt R. Antidepressant-like activity of S20098 (agomelatine) in the forced swimming test in rodents: involvement of melatonin and serotonin receptors. *J. Psychiat. Neurosci.* 29, 126–133 (2004).

26 Papp M, Gruca P, Boyer PA, Mocaer E. Effect of agomelatine in the chronic mild stress model of depression in the rat. *NeuroPsychopharmacol.* 28, 694–703 (2003).

27 Millan MJ, Brocco M, Gobert A, Dekeyne A. Anxiolytic properties of agomelatine, an antidepressant with melanotergic and serotonergic properties: role of 5HT2C receptor blockade *Psychopharmacol* 177, 1–12 (2005).

28 Loo H, Dalery J, Macher JP, Payen A. Pilot study comparing in blind the therapeutic effect of two doses of agomelatine, melatonin agonist and selective 5HT2C receptor antagonist, in the treatment of major depressive disorders. *L'Encephale* 29, 165–171 (2003).

29 Loo H, Hale A, D'haenen H. Determination of the dose of agomelatine, a melatonergic agonist and selective 5HT2C antagonist, in the treatment of major depressive disorder: a placebo controlled dose range study. *Int. Clin. Psychopharmacol.* 17, 239–247 (2002).

30 Montgomery SA, Kennedy SH, Burrows GD, Leyoyeux M, Hindmarch I. Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: a randomized, double-blind, placebo-controlled, discontinuation study. *Int. Clin. Psychopharmacol.* 19, 271–280 (2004)

31 Quera-Salva MA, Vanier B, Chapotot F. Effect of agomelatine on the sleep EEG in patients with major depressive disorders (MDD). *Eur. NeuroPsychopharmacol.* 15(Suppl. 3), S435 (2005).

32 Lam RW. Sleep disturbances and depression: a challenge for antidepressants. *Int. Clin. Psychopharmacol.* 21(Suppl. 1), S25–S29 (2006).

33 Rogoz Z, Skuza G, Kllodzinska A. Anxiolytic and antidepressant-like effects of 7-OH-DPAT, preferential dopamine D3 agonist, in rats. *Pol. J. Pharmacol.* 56, 519–526 (2004).

34 Corrigan MH, Denahan AQ, Wright CE *et al.* Comparison of pramipexole, fluoxetine and placebo in patients with major depression. *Depress. Anxiety* 11, 58–65 (2000).

35 Zarate CA, Payne JL, Singh J *et al.* Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. *Biol. Psychiatry.* 56, 54–60 (2004).

36 Sporn J, Ghaemi SN, Sambur MR *et al.* Pramipexole augmentation in the treatment of unipolar and bipolar depression: a retrospective chart review. *Ann. Clin. Psychiatry* 12, 137–140 (2000).

37 Perugi G, Toni C, Ruffolo G *et al.* Adjunctive dopamine agonists in treatment – resistant bipolar-II depression: an open case series. *Pharmacopsychiatry* 34, 137–141 (2001).

38 Lattanzi L, Dell'Osso L, Cassano P *et al.* Pramipexole in treatment-resistant depression: a 16-week naturalistic study. *Bipolar Disord.* 4, 307–314 (2002).

39 Cassano P, Lattanzi L, Soldani F *et al.* Pramipexole in treatment resistant depression an extended follow-up. *Depress. Anxiety* 20, 131–138 (2004).

40 Anderson IM. SSRIs versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. *Depress. Anxiety* 7(Suppl. 1) 11–17 (1998).

• **Meta-analysis presenting the case that tricyclic antidepressants may be more efficacious in the treatment of certain forms of major depression than selective serotonin-reuptake inhibitors (SSRIs).**

41 Gupta RK, Tiller JWG, Burrows GD. Dual action antidpressants and some important considerations. *Aust. NZ J. Psychiat.* 37, 190–195 (2003).

42 Briley M. New hope in the treatment of painful symptoms in depression. *Curr. Opin. Invest. Drugs* 4, 42–45 (2003).

43 DeBoer T, Nefkens F, van Helvoirt A. The α2-adrenoceptor antagonist Org3770 enhances noradrenergic and 5HT1A mediated serotonergic neurotransmission *in vivo*. *Eur. J. Pharmacol.* 253, R5–R6 (1994).

44 Olver JS, Burrows GD, Norman TR. Third generation antidepressants: do they offer advantages over the SSRIs? *CNS Drugs* 15, 941–954 (2001).

• **Qualitative review of data comparing newer antidepressants with the SSRIs, suggesting that the newest antidepressants are only equal in efficacy to the SSRIs with respect to onset of action, side effects and safety.**

45 Millan MJ, Gobert A, Lejeune F *et al.* S33005, a novel ligand at both serotonin and norepinephrine transporters I: receptor binding, electrophysiological and neurochemical profile in comparison with venlafaxine, reboxetine, citalopram and clomipramine. *J. Pharm. Exp. Ther.* 298, 565–580 (2001).

46 Millan MJ, Dekeyne A, Papp M *et al.* S33005, a novel ligand at both serotonin and norepinephrine transporters II: behavioral profile in comparison with venlafaxine, reboxetine, citalopram and clomipramine. *J. Pharm. Exp. Ther.* 298, 581–591 (2001).

47 Cespuglio R, Rousset C, Debilly G *et al.* Acute administration of the novel serotonin and noradrenaline reuptake inhibitor S33005, markedly modifies sleep–wake cycle architecture in the rat. *Psychopharmacol.* 181, 639–652 (2005).

48 Board F, Persky H, Hamburg DA. Psychological stress and endocrine functions, *Psychosomaticsic Med.* 18, 324–333 (1956).

49 Gibbons JL. Cortisol secretion rate in depressive illness. *Arch. Gen. Psychiat.* 10, 572–575 (1964).

50 Mitchell P, Hadzi-Pavlovic D, Parker G *et al.* Depressive psychomotor disturbance, cortisol and dexamethasone. *Biol. Psychiat.* 40, 941–950 (1996).

51 Arborelius L, Owens MJ, Plotsky PM *et al.* The role of corticotrophin releasing factor in depression and anxiety disorders. *J. Endocrinol.* 160, 1–12 (1999).

52 Deuschle M, Schweiger U, Weber B *et al.* Diurnal activity and pulsatility of the hypothalamus-pituitary-adrenal system in male depressed patients and healthy controls. *J. Clin. Endocrinol. Metab.* 82, 234–238 (1997).

53 Nemeroff CB, Widerlov E, Bisette G *et al.* Elevated concentrations of CSF corticotrophin releasing factor-like immunoreactivity in depressed patients. *Science* 226, 1342–1344 (1984).

54 McQuade R, Young AH. Future therapeutic targets in mood disorders: the glucocorticoid receptor. *Br. J. Psychiat.* 177, 390–395 (2000).

55 Ravaris CL, Sateia MJ, Beroza KW *et al.* Effect of ketoconazole on a hypophysectomised, hypercortisolaemic, psychotically depressed woman. *Arch. Gen. Psychiat.* 45, 966–967 (1988).

56 Murphy BE. Antiglucocorticoid therapies in major depression: a review. *Psychoneuroendocrinology* 22(Suppl. 1), S125–S132 (1997).

57 Wolkowitz OM, Reus VI, Chan T *et al.* Antiglucocorticoid treatment of depression: double-blind ketoconazole. *Biol. Psychiat.* 45, 1070–1074 (1999).

58 Malison RT, Anand A, Pelton GH *et al.* Limited efficacy of ketoconazole in treatment refractory major depression. *J. Clin. Psychiat.* 19, 466–470 (1999).

59 Murphy BE, Filipini D, Ghadirian AM. Possible use of the glucocorticoid receptor antagonists in the treatment of major depression: preliminary results using RU486. *J. Psychiat. Neurosci.* 18, 209–213 (1993).

60 Belanoff JK, Flores BH, Kalezhan M *et al.* Rapid reversal of psychotic depression using mifepristone. *J. Clin. Psychopharmacol.* 21, 516–521 (2001).

61 Hsu SY, Hsueh AJ. Human stresscopin and stresscopin-related peptide are selective ligands for the type 2 corticotropin-releasing hormone receptor. *Nat. Med.* 7, 605–611 (2001).

62 Gilligan PJ, Robertson DW, Zaczek R. Corticotropin releasing factor (CRF) receptor modulators: progress and opportunities for new therapeutic agents. *J. Med. Chem.* 43, 1641–1660 (2000).

•• **Review of the medicinal chemistry of drugs acting at corticotropin-releasing factor receptors, and an exploration of their potential for the treatment of depression and anxiety.**

63 Lelas S, Wong H, Li Y-W *et al.* Anxiolytic-like effects of the corticotrophin- releasing factor 1 (CRF1) antagonist DMP904 [4-(3-pentylamino)-2,7-dimethyl- 8-(2-methyl-4-methoxyphenyl)-pyrazolo-[1,5-a]-pyrimidine] administered acutely or chronically at doses occupying central CRF1 receptors in rats. *J. Pharm. Exp. Ther.* 309, 293–302 (2004).

64 Mansbach RS, Brooks EN, Chen YL. Antidepressant-like effects of CP-154,526, a selective CRF1 antagonist. *Eur. J. Pharmacol.* 323, 21–26 (1997).

65 Arborelius L, Skelton KH, Thrivikraman KV *et al.* Chronic administration of the selective corticotropin-releasing factor 1 receptor antagonist CP-154,526: behavioral, endocrine and neurochemical effects in the rat. *J. Pharm. Exp. Ther.* 294, 588–597 (2000).

66 Hoyberg J, Wik G, Mehtonen OP *et al.* ORG 34517, a selective glucocorticoid receptor antagonist with potent antidepressant activity: first clinical results. *Int. J. NeuroPsychopharmacol.* 5(Suppl. 1), 148 (2002).

67 Zobel AW, Nickel T, Kunzel HEM. Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *J. Psychiat. Res.* 34, 171–181 (2000).

68 Rupniak N, Kramer MS. Substance P and related tachykinins. In: *Neuropsychopharmacology The Fifth Generation of Progress.* Davis KL, Charney D, Coyle JT, Nemeroff CB (Eds). American College of Neuropsychopharmacology 171–177 (2002).

69 Mantyh PD. Neurobiology of substance P and the NK1 receptor. *J. Clin. Psychiat.* 63(Suppl. 1), 6–10 (2002).

70 Kramer MS, Cutler N, Feighner J *et al.* Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science* 281, 1640–1645 (1998).

71 Krishnan KRR. Clinical experience with substance P receptor (NK1) antagonists in depression. *J. Clin. Psychiat.* 63(Suppl. 1), 25–29 (2002).

72 Gold PW, Goodwin FK, Reus VI. Vasopressin in affective illness. *Lancet* 1, 1233–1236 (1978).

73 van Louden L, Goekoop JG, van Kempen GM *et al.* Plasma levels of arginine vasopressin elevated in patients with major depression, *NeuroPsychopharmacol.* 17, 284–292 (1997).

74 de Winter RF, van Hemert AM, DeRijk RH *et al.* Anxious-retarded depression: relation to plasma vasopressin and cortisol. *NeuroPsychopharmacol.* 28, 140–147 (2003).

75 De Bellis MD, Gold PW, Geracioti TD *et al.* Association of fluoxetine treatment with reductions in CSF concentrations of corticotrophin-releasing hormone and arginine vasopressin in patients with major depression. *Am. J. Psychiat.* 150, 656–657 (1993).

76 Ring RH. The central vasopressinergic system: examining the opportunities for psychiatric drug development. *Curr. Pharm. Des.* 11, 205–225 (2005).

•• **Detailed review of the potential for compounds that interact with the vasopressin system to act as antidepressants. More detailed review of data presented in this article.**

77 Ebner K, Wotjak CT, Holsboer F *et al.* Vasopressin released within the septal brain area during swim stress modulates the behavioural stress response in rats. *Eur. J. Neurosci.* 11, 997–1002 (1999).

78 EbnerK, Wotjak CT, Landgraf R *et al.* Forced swimming triggers vasopressin release within the amygdala to modulate stress-coping strategies in rats, *Eur. J. Neurosci.* 15, 384–388 (2002).

79 Serradeil–Le Gal C, Derick S, Brossard G *et al.* Functional and pharmacological characterization of the first specific agonist and antagonist for the V1b receptor in mammals. *Stress* 6, 199–206 (2003).

80 Tanoue A, Ito S, Honda K *et al.* The vasopressin V1b receptor critically regulates hypothalamic-pituitary-adrenal axis activity under both stress and resting conditions. *J. Clin. Invest.* 113, 302–309 (2004).

81 Griebel G, Simiand J, Stemmelin J *et al.* The vasopressin V1b receptor as a therapeutic target in stress related-related disorders. *Curr. Drug Target CNS Neurol. Disord.* 2, 191–200 (2003).

82 Griebel G, Simiand J, Serradeil-Le Gal C *et al.* Anxiolytic-and antidepressant-like effects of the non-peptide vasopressin V1b receptor antagonist SSR149415 suggest an innovative approach for the treatment of stress-related disorders. *Proc. Natl Acad. Sci. USA* 99, 6370–6375 (2002).

83 Nowak G, Trullas R, Layer RT *et al.* Adaptive changes in the N-methyl-D-aspartate receptor complex after chronic treatment with imipramine and 1-aminocycloprpane carboxylic acid. *J. Pharm. Exp. Ther.* 265, 1380–1386 (1993).

84 Paul IA, Layer RT, Skolnick P *et al.* Adaptation of the NMDA receptor in rat cortex following chronic electroconvulsive shock or imipramine. *Eur. J. Pharmacol.* 247, 305–311 (1993).

85 Skolnick P. Antidepressants for the new millennium. *Eur. J. Pharmacol.* 375, 31–40 (1999).

86 Skolnick P. Modulation of glutamate receptors: strategies for the development of novel antidepressants. *Amino Acids* 23, 153–159 (2002).

•• **Material canvassed in the present review is also presented in this article.**

87 Pacher P, Kecskemeti V. Trends in the development of new antidepressants: is there light at the end of the tunnel? *Curr. Med. Chem.* 11, 925–943 (2004).

88 Redrobe JP, Dumont Y, Quirion R. Neuropeptide Y (NPY) and depression: from animal studies to the human condition. *Life Sci.* 71, 2921–2937 (2002).

89 Stogner KA, Holmes PV. Neuropeptide-Y exerts antidepressant-like effects in the forced swim test in rats. *Eur. J. Pharmacol.* 387, R9–R10 (2000).

90 Qu D. A role for melanin-concentrating hormone in the central regulation of feeding behaviour. *Nature* 380, 243–247 (1996).

91 Sato Y. Molecular characterization of the melanin-concentrating-hormone receptor. *Nature* 400, 265–269 (1999).

92 Borowsky B, Durkin MM, Ogozalek K *et al.* Antidepressant, anxiolytic and anorectic effects of a melanin-concentrating hormone-1 receptor antagonist. *Nat. Med.* 8, 825–830 (2002).

93 Duman RS. Depression: a case of neuronal life and death? *Biol. Psychiat.* 56, 140–145 (2004).

•• **Draws together the preclinical and clinical evidence for the neurogenesis hypothesis of depression.**

94 Hashimoto K, Shimizu E, Iyo M. Critical role of brain-derived neurotrophic factor in mood disorders. *Brain Res. Rev.* 45, 104–114 (2004).

95 Shirayama Y, Chen ACH, Nakagawa DS *et al.* Brain-derived neurotrophic factor produces antidepressant effects in behavioural models of depression. *J. Neurosci.* 22, 3251–3261 (2002).

96 Siuciak JA, Lewis DR, Wiegand RM *et al.* Antidepressant like effect of brain derived neurotrophic factor (BDNF). *Pharmacol. Biochem. Behav.* 56, 131–137 (1997).

Affiliations

- *Trevor R Norman*
  University of Melbourne,
  Department of Psychiatry, Austin Hospital,
  Heidelberg 3084, Victoria, Australia
  Tel.: +61 3 9496 5511
  Fax: +61 3 9459 0821
  trevorrn@unimelb.edu.au
- *Graham D Burrows*
  University of Melbourne,
  Department of Psychiatry, Austin Hospital,
  Heidelberg 3084, Victoria, Australia
  Tel.: +61 3 9496 5665
  Fax: +61 3 9496 3976
  graham.burrows@austin.org.au