CLINICAL
INVESTIGATION

Future perspectives on the pharmacological management of depression

Major depressive disorder is a disabling condition that impacts on function and well-being. It is one of the leading causes of disease burden in high-income countries. Treatment of this disorder can be challenging because a significant minority of patients do not respond to initial pharmacotherapy. There has been on-going debate about the 'efficacy' of antidepressants given a large placebo response in trial data. In this nonsystematic review this is discussed and recent studies are quoted that point to more effective ways in interpreting antidepressant randomized controlled trial data. An analysis of recent studies that impact on current clinical practice is also presented, including studies of Agomelatine, antidepressant combinations and augmentation strategies. Studies that may pave the way to more effective treatments and a better understanding of the pathophysiology of this disabling condition are highlighted. These include introduction of triple reuptake inhibitors, NMDA receptor antagonists and glucocorticoid receptor antagonists.

Sarah Yates, Eleanor Smith, Hamid A Alhaj & R Hamish McAllister-Williams*

Academic Psychiatry, Campus for Ageing and Vitality, Westgate Road, Newcastle upon Tyne, NE4 6BE, UK
*Author for correspondence:
Tel.: +44 191 256 3200
Fax: +44 191 256 3324
E-mail: r.h.mcallister-williams@ncl.ac.uk

Major depressive disorder (MDD) is characterized by episodes of low mood with associated symptoms of loss of interest, anhedonia, anergia, sleep and appetite disturbance, poor concentration and memory, pessimistic thoughts regarding the future and recurrent thoughts of death. The impact of depression on individuals can be profound with marked impairments in occupational and social functioning [1], as well as increases in mortality not only as a result of suicide but also due to increase in death from somatic causes, including an approximate doubling in the risk of death from cardiovascular disease [2,3]. As a result, according to the WHO, MDD is associated with the largest burden of disease in the developed world compared with all other disorders, both psychiatric and physical [4]. The management of depression can be multifactorial, employing a variety of psychosocial interventions, psychotherapy and medication. Guidelines such as those produced by the UK's NICE and the British Association for Psychopharmacology recommend the routine prescription of antidepressants for patients with moderate to severe depression, and consideration of their use in those with less severe illness that is persistent [5,6]. Most commonly, selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine or citalopram, are prescribed as first-line treatment. A significant minority of patients do not respond to initial pharmacotherapy [7] and hence strategies are necessary for patients with 'treatment refractory depression'.

Despite the recommendations of various guidelines, and observations of increasing prescription of antidepressants [8], in recent years there has been some controversy regarding their use. In particular, a publication in 2008 by Kirsch and colleagues argued, on the basis of a meta-analysis of data from randomized controlled trials (RCTs) of antidepressants in MDD, that the drugs were not clinically significantly

FUTURE SCIENCE

part of fsg

superior to placebo except in those patients with very severe depression [9]. As a result, these researchers questioned the use of antidepressants in the majority of depressed patients.

In this nonsystematic review, recent research has been considered, focusing on RCTs of treatment in unipolar depression, particularly those published since 2010. The review is divided into three sections. The first discusses recent analyses regarding the evaluation of antidepressants in placebo-controlled RCTs in the context of the concerns raised by Kirsch (2008). This relates to the fundamental question of the utility of antidepressants in the management of MDD. The second section considers recently published data that relates to currently available medication and hence that has a potential impact on current clinical practice. The third section of the review considers data relating to treatments not yet licensed for use and considers future prospects for the pharmacological management of MDD.

Do antidepressants work in patients with MDD?

The conclusions drawn by the meta-analysis of Kirsch *et al.*, titled 'Initial Severity and Antidepressant Benefits', published in 2008, have been challenged by a number of authors [10–14]. Much of the criticism is focused on the methods of analysis used by Kirsch *et al.* with some authors re-analyzing the data. The related issue of how data in clinical trials is analyzed is also considered in this section.

■ Analysis conducted by Kirsch *et al.*

The data used in the Kirsch *et al.* meta-analysis came from 35 RCTs of four antidepressants (venlafaxine, fluoxetine, paroxetine and nefazodone) in MDD held by the US FDA. This has the advantage in that it avoids the potential of publication bias. Turner and colleagues have demonstrated a significantly larger effect size for the effect of antidepressants versus placebo in MDD RCTs in published studies versus those submitted to the FDA [15]. The method of analysis used by Kirsch *et al.* entailed pooled data from active-treatment arms being compared with pooled data from placebo arms. A fixed-effects analysis to weight the RCT's included in the meta-analysis, which assumes that the effect being estimated is constant across the sample, was also used. With regard to the effect size, while Kirsch did analyze mean differences in depression rating scale scores (they used the Hamilton Depression Rating Scale [HDRS]), their primary analysis utilized standardized differences – Cohen's d.

The main findings of the analysis by Kirsch *et al.* were that, overall, while there was a statistically significant effect of antidepressants across all of the trials, they argued that the effect was not clinically significant.

The difference in mean HDRS for drug and placebo was 1.80 or a standardized effect difference of d = 0.32 (note there was difference between the four drugs studied with d = 0.21, 0.22, 0.42 and 0.47 for nefazodone, fluoxetine, venlafaxine and paroxetine, respectively). Kirsch *et al.* cited as a bench mark for clinical significance NICE depression guidelines (CG 23), published in 2004, which suggested a clinically significant difference between antidepressant and placebo would be three points on the HDRS or d = 0.5. Another major finding of Kirsch *et al.* was a significant effect of baseline depression severity on the drug–placebo difference. In their analysis, while drug response remained relatively consistent, there was a decrease in placebo response with increasing severity, and hence increasing drug–placebo difference. From this analysis they determined that the standardized difference did not reach NICE's cut off of 0.5 until the baseline HDRS was above 28, which Kirsch *et al.* described, on the basis of a published statement by the American Psychiatric Association, as 'very severe'. This led to their conclusion that antidepressants are only of clinical utility in those few patients with the very severest depression.

■ Criticisms of the Kirsch *et al.* analysis & conclusions

The actual methods used by Kirsch *et al.* in their analysis have been criticized by many. For example, the use of pooled data has been criticized by Horder *et al.* who pointed out that standard meta-analytical practice is to compare the difference between active treatment and placebo within each trial before averaging these differences [13]. This paper also criticized the use of a fixed effect analysis, given the heterogeneous nature of the trials included in the analysis. They suggested that the magnitude of the effect of antidepressants may well vary between trials and as such random-effects weighting, which does not make this assumption, should be used in a meta-analysis. These concerns are reiterated by Fountoulakis and Möller who suggest that the pooled effect size should be calculated by weighting sample size or the inverse of the variance [12]. Since all of the trials included in the meta-analysis used HDRS scores as an outcome measure, Horder *et al.* question the use of Cohen's d as the primary measure of effect size in the Kirsch analysis. Their argument was that although standardized effects sizes are useful when trials do not share a common outcome measure this is not the case in the data set used. Therefore, the use of difference in HDRS scores would be more powerful and is in line with Cochrane recommendations [201]. Both Horder *et al.* and Fountoulakis and Moller have re-analyzed the data examined by Kirsch and found drug–placebo differences of between 2.18 and 2.70 HDRS points

(compared with 1.80 by Kirsch *et al.*). They also found that this difference was above the NICE stated threshold of 3 for both venlafaxine and paroxetine. Kirsch and his colleagues have responded to these criticisms of their analysis and stand by their findings [16] .

With regard to the findings in relation to the impact of baseline severity, there is also lack of consensus. Horder *et al.,* in their re-analysis of Kirsch's data found that the response to placebo was relatively independent of baseline severity while the effect of antidepressants increases with severity [13]. Using a different data set of fluoxetine and venlafaxine data, Gibbons *et al.* found no effect of baseline severity on antidepressant placebo differences at all [17]. This was similar to the finding of Melander *et al.* who examined a large set of data submitted to the European Medicines Agency [18].

■ **Interpreting results from clinical trials: responders & nonresponders?**
In the critic by Horder *et al.* of the Kirsch *et al.* analysis, they conclude that "*the true lesson of the present controversies may be not that antidepressants do not work very well, but that antidepressant research does not work very well*" [13]. One of the key issues here is that using mean differences in rating scale scores potentially obscures differences in responses between patients. This may well be due to the specific effects of treatments being somewhat smaller than the nonspecific effects seen with any treatment including placebo [19]. The finding of Kirsch *et al.* that the standardized effect size for the difference between drug and placebo is <0.5 [9], which had been set by NICE as the cut off for clinical significance, is confirmed in other analyses such as that by Turner *et al.* taking publication bias into account [15]. However, from the perspective of an individual doctor with an individual patient, it is more important to consider the chances that the patient will respond or remit rather than the mean difference in rating scale score across a population. As a result, some argue that response- and remission-rate differences between drug and placebo are more clinically meaningful [18]. However, this is not an approach employed by NICE since they have accepted the argument made to them by Kirsch that significant differences in rates of patients achieving some categorical end point can arise through a trivial difference in mean rating scale score [20]. This argument is predicated on the distribution of rating scale scores being unimodal.

In the context of this debate, Thase *et al.* have questioned whether current methods of analyzing antidepressant trial data are appropriate and consider whether antidepressant efficacy is better understood as a large effect in a subgroup of patients who respond to treatment [21]. To explore this issue, they examined data pooled from five RCTs of escitalopram versus placebo using standard methods (analysis of covariance) based on an assumption of a unimodal distribution of rating scale scores and a mixed analysis assuming a bimodal distribution. The standard methods assume that baseline scores are normally distributed and that treatment interventions cause the distribution to be shifted laterally. The bimodal mixture allows for a flexible shape of the distribution of observed depression rating scale scores and examines the change in this distribution with treatment. In the data examined, all trials used the Montgomery-Asberg depression rating scale (MADRS) as a primary outcome measure at week 8, with remission defined as MADRS score of ≤10 or ≤12 and response as ≥50% reduction from baseline MADRS score. The mixture model better described the distribution of week 8 MADRS scores and was a better predictor of observed response and remission rates. Thase *et al.* concluded that reporting small mean differences in rating scales potentially *"obscure large and clinically meaningful responses for a subgroup of patients with depression"* including in some patients with 'less severe' depression.

From a similar perspective, Gueorguieva *et al.* studied pooled data from seven RCTs of duloxetine and comparator SSRIs [22]. Specifically, they statistically examined the trajectory of change of individual patients. While those treated with placebo could not be statistically separated from a single trajectory, those treated with antidepressants fell into two groups; those with a trajectory of response (76.3% of the sample treated with active-drug) and those with a trajectory of nonresponse (23.7% of the sample). While those who responded did better than those treated with placebo, the active drug nonresponders actually did far worse than placebo-treated patients. In addition, by separating out responders and nonresponders to medication demonstrated a much larger effect of drugs in those who respond than normally seen in standard RCT analyses. The drug–placebo difference for responders in the Gueorguieva *et al.* study was over 4.5 HDRS points, while that between responders and nonresponders all given medication was over 11 HDRS poins. As the authors point out, the fact that the trajectory of nonresponders in the active drug group was worse than those on placebo may contribute to the problem of demonstrating antidepressant efficacy in clinical trials and that by presenting results as a group mean, the positive impact on those who respond may be minimized by the unchanged or negative impact on those that do not.

Conclusions
In some people's eyes the question of efficacy of antidepressants in MDD remains a contentious issue. Several points are however worth making. First, the

argument of Kirsch *et al.* on the lack of clinically significant effects of antidepressants was based on completely arbitrary criteria for clinical significance set out by NICE in CG24, published in 2004. It is important to note that the revision of these guidelines published in 2009 (CG90) continues to argue that antidepressants are appropriate first-line treatments for patients with at least moderate severity MDD, but they have dropped their previous definitions of clinical significance [6]. This is an acceptance in part that RCTs are not specifically designed to assess clinical significance, as opposed to simply being research tools to statistically test hypothesis that a treatment works [10]. Second, the conclusions drawn by Kirsch that if antidepressants are of any use at all, they are just for those patients with very severe depression, is also challenged by other studies that do not find effects of baseline severity on degree of response [17,18]. The importance of this is critical since it has influence in terms of which depressed patients should be recommended to be treated with antidepressants. Third, the novel analytical approaches to antidepressant RCT data employed by Thase *et al.* and Gueorguieva *et al.* also point to the potential need to move away from current simple analysis techniques when assessing whether or not a drug is effective in at least some patients [21,22]. Fourth, differentiating the pharmacological effect of a drug from placebo will always be challenging in a relapsing/remitting condition, such as MDD where the effect size of placebo is large (~ 0.5) and certainly greater than no treatment or watchful waiting.

The bottom line is that prescription of placebo is not ethically accepted and there is at the very least a statistically significant greater effect of active drug over placebo. As a result, treatment guidelines continue to recommend antidepressants for patients with moderate to severe depression.

Recent clinical trials of currently available treatments

This section reviews recently published clinical trials relating to currently available (and licensed – though with some being used 'off label') treatments and so hence with the potential to impact on current prescribing practice.

■ Agomelatine

Agomelatine (Valdoxan®) is a synthetic melatonin analogue initially evaluated for its beneficial effects on sleep. It is known to be an agonist at melatonergic MT_1 and MT_2 receptors and an antagonist at serotonin $5HT_{2C}$ receptors [23], and has been shown to have efficacy as an antidepressant [24,25]. Stahl *et al.* performed an 8-week, multicenter, double-blind, parallel-group trial in 503 patients randomly allocated on a 1:1:1 basis to agomelatine 25 mg, agomelatine 50 mg or placebo, daily [26]. In terms of reduction in HDRS scores, agomelatine 25 mg separated from placebo at all-time points as did the 50 mg dose (with the exception of the final 8 week assessment). Both doses were associated with a significantly higher rate of response and remission compared with placebo. Similarly, Zajecka *et al.* conducted an identically designed study in 511 patients [27]. They reported significantly superior efficacy of agomelatine 50 mg compared with placebo in terms of reductions in HDRS score and response and remission rates. The 25 mg dose, however, did not separate from placebo. Notably, agomelatine was also associated with significant improvements in sleep and the drug was extremely well tolerated. However, clinically notable transient aminotransferase elevations were observed in 4.5% of those treated with agomelatine 50 mg. In terms of relapse prevention, a 24-week double-blind, placebo-controlled trial by Goodwin *et al.* assessed the long-term antidepressant effect of agomelatine treatment [28]. Patients who had been responsive to 8–10 weeks of agomelatine treatment were randomized to continue on the drug (n = 165) or switch to placebo (n = 174) for an additional 6-month period. By 10 weeks post-randomization, there was a statistically significant difference between treatments with a 12% lower rate of relapse with agomelatine compared with placebo treatment. At 6 months, the relapse rate was 22% in the agomelatine group and 47% in the placebo group.

On the basis of these acute- and long-term data, agomelatine received a marketing authorization for the treatment of major depressive episodes in adults in February 2009 by the European Medicines Agency. One requirement stated in the Summary of Product Characteristics is that liver function tests should be performed before prescription of the drug and then at 3, 6, 12 and 24 weeks.

There have been several randomized, double-blind studies comparing agomelatine with other antidepressants, three have been published to date. A venlafaxine comparator trial compared a fixed dose of agomelatine 50 mg with venlafaxine XR 150 mg in 276 patients with depression [29]. The primary outcome was sexual function, which was significantly better on agomelatine compared with venlafaxine. Antidepressant efficacy was similar in the two treatment groups in terms of mean decrease in MADRS scores as well as response and remission rates. The antidepressant effects of sertraline (50–100 mg; n = 159) versus agomelatine (25–50 mg; n = 154) has also been compared in a 6-week trial [30]. The primary outcome was circadian rest–activity cycles. This, plus sleep, improved more with agomelatine compared with sertraline. There was also a significantly greater reduction in HDRS score

with agomelatine. The most recently published comparator study was conducted in patients with severe depression (HDRS at least 25) and treated with either flexible dose agomelatine (25–50 mg; n = 252) or fluoxetine (20–40 mg; n = 263) [31]. The primary outcome was reduction in HDRS score and agomelatine was found to be significantly superior to fluoxetine with a difference in mean scores at end point of approximately 1.5 points (see above for discussion regarding the clinical significance of this).

Conclusions

The data obtained to date suggest that agomelatine is an effective antidepressant with at least comparable efficacy to currently used treatments. It is also extremely well tolerated being free of weight gain or sexual side effects common to other frequently used antidepressants [32]. This is supported by a large naturalistic study in over 3000 patients in Germany [33]. However, while agomelatine was approved by the European Medicines Agency in July 2011, NICE stated that it was unable to recommend UK NHS use of agomelatine for the treatment of major depressive episodes because no evidence submission was received from the manufacturer of agomelatine (Servier [Neuilly-sur-Seine, France]). This, coupled with the cost of agomelatine versus the current first line prescription of SSRIs, has led local prescribing committees in the UK to restrict the use of agomelatine to a third- or fourth-line agent. The NHS uses a 'traffic light system' for the classification of medicines and agomelatine is classified as 'red' in some areas indicating that it can only be prescribed, within secondary or tertiary services. Its true place within the pharmacological armamentarium for the management of depression, remains unclear but it may be of particular use in patients not tolerant of other medications and/or those with marked circadian disturbances.

■ Vilazodone

Vilazodone is a dual-acting serotonergic drug that blocks 5-HT re-uptake and, in addition, acts as a 5-HT_{1A} receptor agonist. The drug therefore combines the effects of an SSRI with direct 5-HT_{1A} activation. In two published 8-week Phase III trials involving a total of 878 adults with MDD, vilazodone demonstrated significant improvements relative to placebo use [34]. It was therefore approved for the treatment of MDD by the FDA in January 2011; however, it is not available for use within Europe.

■ Antidepressant combinations

The notion of using combinations of antidepressants for patients with severe treatment refractory depression has been around for almost as long as we have had antidepressants. Initially clinicians combined the two original classes – monoamine oxidize inhibitors and tricyclic antidepressants – a combination that required great care due to risks of toxicity [35]. In more recent years there has been interest in combinations of drugs with theoretically complementary mechanisms of actions, particular the use of mirtazapine (which leads to an increased release of 5-HT and noradrenaline [NA]) and either an SSRI or a serotonin and NA reuptake inhibitor (SNRI) such as venlafaxine (the latter being nicknamed 'Californian rocket fuel' by one of the doyens of world psychopharmacology, Steven Stahl). Unfortunately until recently there have been fewer data to support the use of such combinations with most of the studies being small and/or not placebo controlled [36–38]. However two further recent studies have addressed this issue.

The first of these studies is of interest since it was not conducted in treatment refractory patients, but rather studied the effects of treatment given first line [39]. This was based on a hypothesis that it may be important to treat patients from the out-set with the most effective medications. The study was in 105 depressed patients randomized to one of four treatment arms, being fluoxetine 20 mg compared with mirtazapine 30 mg plus fluoxetine 20 mg, venlafaxine 225 mg or buproprion 150 mg daily. The authors found a significant difference in mean end point HDRS score at 6 weeks with all three combinations being superior to fluoxetine monotherapy by approximately 4.5 points. There was, however, no difference in response rates between the four treatments (fluoxetine monotherapy, 54%; mirtazapine plus fluoxetine, 68%; mirtazapine plus bupropion, 65%; mirtazapine plus venlafaxine, 73%), although this may have related to a lack of statistical power given that there were only 25–28 in each treatment arm. An interesting observation was that in those who made a substantial response, double-blind discontinuation of one of the treatments led to a relapse in approximately 40%. There was little difference in terms of tolerability between the four treatments.

These findings contrast with research by Rush *et al.* who conducted the CO-MED study [40]. This was a three-arm study comparing the efficacy of escitalopram plus placebo (monotherapy) with buproprion plus escitalopram and venlafaxine plus mirtazapine. Dosage of all medication was flexible (being up to 20 mg for escitalopram, 400 mg for bupropion, 45 mg for mirtazapine and 300 mg for venlafaxine). This is by far the largest RCT of combined antidepressants published to date, with 665 patients randomized – meaning approximatelty 220 in each treatment arm. The overall finding of this research was that the treatment groups did not differ in either remission or response rates (51.6–52.4%) at 12 weeks. The study continued onto 7 months following

randomization and all outcome variables remained no different between groups (response rates 57.4–59.4%). In terms of tolerability, the venlafaxine–mirtazapine group had a significantly higher side-effect burden. The lack of difference in efficacy between the three treatments has also been shown in *post hoc* analysis in those with melancholic depression [41] and those with more severe depression [42]

Conclusions

Prior to the advent of the Co-MED study there had been a range of small studies that had supported the use of combinations of antidepressant, particularly mirtazapine with SSRIs or SNRIs, or at least did not argue against their use. The question now is whether the situation is different following the negative results in by far the largest study. A potentially important issue is the relative comparability of the various studies, particularly in relation to the nature of the patients being treated. This is hard because of differences in the ways that demographic details have been reported. The mean age of the patients in the Blier *et al.* study was approximately 44 [39], which is similar to that in the Co-MED study [42] as were baseline HDRS scores (22 and 24, respectively). The patients in the Co-MED study were more likely to have recurrent depression (78% vs 63%). Given the aim of the Blier *et al.* study to examine effects of different treatment from treatment initiation, the patients studied appeared to have had shorter durations of illness (still with 61% at least 1 year, but compared with 55% with a current episode of at least 2 years and a mean duration of 61 months in the Co-MED study). The patients in the Blier *et al.* study were also more likely to be melancholic (76 vs 20%). One stricking feature of patients in the Co-MED study, for which there is no data reported by Blier *et al.*, is that 45% of patients had an onset of depression before the age of 18 with a mean age of first episode being 24. High rates of childhood abuse were also reported. These comparisons lead to more questions than answers. Several other differences exist between the Blier *et al.* study and the Co-MED study that might explain the conflicting results and conclusions [43,44]. Importantly the Co-MED study was single blind (the prescribers were aware of what drugs and doses were being prescribed) while the Blier *et al.* study was double blind. A further difference was the doses used in the two studies. While in the Co-MED study patients treated with venlafaxine and mirtazapine combination received mean doses of 192 mg and 20 mg/day, respectively, in the Blier *et al.* study, similarly treated patients received 225 mg and 30 mg. There is a concern that in the Co-MED study patients were being given sub-therapeutic doses, particularly of mirtazapine.

Another important observation comparing the studies is that the remission rate in the monotherapy arm in Co-MED was 38.8%, whereas in the Blier *et al.* study it was 25%. It is unclear why such a difference exists. It might have related to the patients in Co-MED either receiving a more efficacious monotherapy (escitalopram 20 mg vs fluoxetine 20 mg) or that the patients were generally more likely to respond. It is also important to consider the differences between a large multicenter RCT such as Co-MED and a single center study such as that conducted by Blier *et al.* Coryell has pointed out that there may be some loss in precision associated with large-scale multicenter clinical trials due to the variance between sites [44].

Prior to the publication of the Co-MED data, many guidelines from around the world for the management of treatment refractory depression included recommendations for consideration of the use of mirtazapine in combination with SSRIs or SNRIs [5,6,45,46]. It remains to be seen how guideline development groups revising these recommendation deal with the new evidence.

■ **Antidepressant augmentation strategies**

Similar to combinations of antidepressants, for decades clinicians have been adding an antipsychotic to an antidepressant when managing patients with MDD. This has not just been for patients with psychotic symptoms, but variously used to treat comorbid anxiety symptoms and/or in an attempt to gain a response in an otherwise nonresponsive patient. In the last few years there have been several RCTs of the efficacy of second-generation (atypical) antipsychotic (SGA) augmentation of antidepressants. Nelson and Papakostas analyzed 16 placebo-controlled RCTs and found a highly significant effect in favor of atypical antipsychotic augmentation though at the expense of worse tolerability [47]. One of the studies included in this meta-analysis was a large study by El-Khalili *et al.* [48]. This was an 8-week, double-blind, randomized, parallel-group, placebo-controlled trial involving 446 patients recruited from 56 centers. It was designed to evaluate once-daily quetiapine modified release (XR) as augmentation treatment in patients with MDD and a history of inadequate response to ongoing antidepressant therapy. Patients were randomized in a 1:1:1 ratio to one of three treatment regimens in addition to ongoing antidepressants (mainly SSRIs or SNRIs); quetiapine XR 150 mg per day, quetiapine XR 300 mg per day or placebo. The primary end point was change in the MADRS total score. This was shown to be significantly greater with quetiapine XR 300 mg than with placebo. Mean MADRS total score was also reduced with quetiapine XR 150 mg at week 6, but this difference was not statistically significant compared with placebo. The percentage of patients

who withdrew from the study was higher in the groups receiving quetiapine, mostly due to sedation and somnolence. Rates of adverse events related to extra-pyramidal side effects were low.

A similar study was conducted by Bortnick *et al.* [49]. This was again an 8-week study in 310 patients. Patients were randomized to either quetiapine XR 150 mg or placebo. However, at week 2 the dose of quetiapine was up-titrated to 300mg. At the end of 8 weeks there was a significant 3.4 point difference in mean MADRS score between quetiapine and placebo. In addition, there was a significant difference at week 1 before dose up-titration. However, drops due to side effects were significantly higher in the quetiapine treated patients (9.9 vs 2.6%). On the basis of these, plus additional data, the European Medicines Agency grated a marketing authorization for quetiapine XR as add on therapy for patients with suboptimal response to antidepressants in April 2010.

Aripiprazole is a SGA with a novel mechanism of action, being a dopamine (DA) receptor partial agonist. It also differs from other SGAs in that it is generally not sedative and can, if anything, be rather activating. Given that many patients with depression are anergic, it is of interest that three large, multicenter, randomized, double-blind, placebo-controlled studies have investigated the efficacy of aripiprazole augmentation of antidepressants [50–52]. The data from the two earlier studies has been pooled by Reimherr *et al.* [53]. Both of these previous double-blind 6-week RCTs have demonstrated a significant advantage of aripiprazole (flexible doses between 2 and 20 mg: mean 11 mg/day) over placebo as an 'add-on' treatment in patients who had failed at least one trial of an antidepressant retrospectively and one prospective trial of an SSRI. The advantage of the Reimherr *et al.* analysis was that by pooling the data from all 724 patients it was possible to analyze (*post hoc*) the effect of aripiprazole on the full range of depressive symptoms by undertaking an item analysis on the MADRS. Aripiprazole demonstrated an advantage in eight of the ten items. This strongly supported the notion that the drug has an effect on the core symptoms of depression rather than simply a nonspecific activating effect. In November 2007, the FDA approved the use of aripiprazole as an augmentation treatment in MDD. Subsequently, the data were considered by the European Medicines Agency in June 2009 but a marketing authorization was not granted because of concerns that included *"the lack of controlled data to establish the duration of treatment and the maintenance of the efficacy"* (see 'Withdrawal Letter' [202]). The company involved in marketing the drug (Bristol-Myers Squibb) have subsequently taken a decision not to pursue this indication within Europe.

In conclusion, there is growing evidence for the use of SGAs as augmentation agents in the management of patients with MDD nonresponsive to antidepressants. The strongest data showing benefit are for quetiapine and aripiprazole, although the latter lacks controlled continuation data. Both are licensed for this use in the USA, however, only quetiapine is licensed in Europe. Given that the drugs have very different side-effect profiles, the former sedative and the later activating, they do potentially offer very different options in the management of patients. There remains uncertainty as to the relative efficacy between these two drugs compared with other treatments such as lithium, which has long been used as an augmentation agent. A RCT has been conducted comparing lithium and quetiapine as augmentation agents. To date, this is yet to be published in full. However the data are reported to show that in patients with lithium levels of at least 0.6 mmol/l, there is no significant difference in the efficacy of the treatments [Bauer M, Pers. Comm.].

Potential future pharmacotherapeutic options

This section explores examples of future therapeutic avenues based on recently published trials of potentially yet to be licensed medications. A number of these compounds revisit 'the monoamine hypothesis of depression' by targeting the 'conventional' pathways known to be implicated in the mechanisms of actions of antidepressants in current use, namely the 5-HT, NA and DA systems. Other compounds build upon recently developed ideas regarding the involvement of different systems, such as glutamate, GABA, acetylcholine and neurosteroids in the pathophysiology and psychopharmacology of depression.

■ Vortioxetine

Vortioxetine (Lu-AA21004; (1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine)) is a novel 'multimodal' antidepressant drug currently under development by Lundbeck [54,55]. It binds to human 5-HT_{1A} and 5-HT_{1B} receptors acting as a near-full and partial agonist, respectively. It also acts as an antagonist at 5-HT_3 and 5-HT_7 receptors and an inhibitor of the 5-HT transporter (SERT). In rodents, vortioxetine has been shown to increase the extracellular concentrations of 5-HT, NA and DA in the prefrontal cortex and the hippocampus [56]. It has been investigated in a multicenter RCT with an active reference of venlafaxine [55]. In this Lundbeck-sponsored, 6-week, Phase II clinical trial, 429 adult patients with a major depressive episode were randomized to receive 5 or 10 mg vortioxetine, placebo or venlafaxine XR 225 mg. The therapeutic antidepressant effect of both doses of vortioxetine were comparable with venlafaxine XR and significantly better than placebo. This was the case in relation to both depressive and anxiety symptoms. It is intriguing that

the dose of 5 mg vortioxetine was shown to be effective although such a dose leads to approximately 40% occupancy of SERT sites [56]. This indicates that additional pharmacological mechanisms may be involved in the antidepressant therapeutic effect. In another RCT of 766 depressed patients treated with placebo, vortioxetine or the active comparator duloxetine, neither active treatment was superior to placebo on the primary outcome measure, although there were some significant effects of both drugs on a number of subscales of depression measures [57]. These results are not entirely surprising given the large number of (often unpublished) failed antidepressant RCTs and the difficulties inherent in analyzing RCT data described in the first section of this review. Another Lundbeck-sponsored trial investigated vortioxetine at a daily dose of 5 mg in elderly depressed patients compared with placebo and duloxetine 60 mg daily [58]. In this study, vortioxetine as well as duloxetine were superior to placebo on the primary outcome measure (reduction in HDRS score) compared with placebo. Of potential note, vortioxetine treatment led to improvements in various cognitive functions including processing speed, verbal learning and memory. The dropout rate due to side effects was lower for vortioxetine than duloxetine. In addition, the only side effect that demonstrated significantly higher incidence on vortioxetine compared with placebo was nausea. Taken together, the results of these trials are promising and indicate efficacy and tolerability of vortioxetine. On the basis of this, Lundbeck have submitted an application for approval to the European Medicines Agency in September 2012.

■ DA receptor ligands and 5-HT, NA, DA triple reuptake inhibitors

The introduction of the SSRIs was revolutionary since their pharmacological selectivity led to minimizing adverse events seen with more 'dirty' pharmacological drugs such as the older tricyclic antidepressants. However, questions remain about the relative efficacy of the 'cleaner' SSRIs, with evidence that SNRIs have greater efficacy compared with SSRIs, particularly in those with severe depression [59]. This raises the question that perhaps drugs with effects on monoaminergic transmission beyond simply a selective effect on 5-HT may have greater efficacy. In addition to noradrenergic transmission that is influenced by SNRIs, there is evidence that dopaminergic dysregulation may be implicated in a number of depressive symptoms, such as anhedonia, lack of energy, poor motivation and neurocognitive impairment [60–62]. Currently however, dopaminergic neurotransmission is generally not considered as a target for antidepressant treatment. However, the DA and NA reuptake inhibitor bupropion has been in use as an effective antidepressant for over 20 years [63,64]. Furthermore, pramipexole, which is a DA-D$_2$, -D$_3$ and -D$_4$ receptor agonist used in Parkinson's disease, has shown efficacy in treating major depression [65].

More recently, 5-HT, NA and DA reuptake inhibitors, also known as triple reuptake inhibitors, have been under development as new-generation antidepressants. An example of such a drug is amitifadine (also known as EB-1010; DOV21947), which is a serotonin-preferring triple reuptake inhibitor developed by Euthymics Bioscience Inc. (Cambridge, MA, USA). In a multicenter RCT, Tran *et al.* studied the efficacy and tolerability of a 6-week course of amitifadine in 63 patients with MDD, initiated at a daily dose of 50 mg and titrated up to a daily dose of 100 mg, compared with placebo [66]. Amitifadine demonstrated a significant superiority to placebo with a difference of approximately 4 points on end point MADRS score and an effect size of 0.6 (Cohen's d). In addition, amitifadine significantly improved anhedonia, a core symptom of major depression thought to relate to DA dysregulation. Amitifadine was well tolerated with just two patients (6%) on amitifadine and two patients (7%) on placebo discontinuing treatment due to adverse events. This proof-of-concept small-size study provided initial evidence of antidepressant effect and good tolerability of amitifadine, although larger scale studies are clearly still required.

A concern with drugs that block DA transporters is their potential for abuse. This has been addressed in a study by Schoedel *et al.* [67]. They analyzed the abuse potential of the triple reuptake inhibitor tesofensine, compared with placebo, D-amphetamine, bupropion and atomoxetine in recreational stimulant users. The effects of tesofensine were not significantly different from those of placebo. The results showed that, certainly for the triple uptake inhibitor tesofensine, blockade of DA uptake appears unlikely to be associated with recreational abuse.

■ Glutamate

There are a number of reasons to consider a possibility for a role of glutamate in the pathophysiology and treatment of depression. First, changes in glutamate levels in plasma and cerebral spinal fluid have been shown in patients with mood disorders [68–70]. Second, functional neuroimaging studies using proton magnetic resonance spectroscopy have demonstrated decreased glutamate concentrations in the anterior cingulate cortex of patients with major depression [71]. Third, traditional antidepressants such as tricyclic antidepressants and SSRIs have been shown to decrease the function of the glutamate NMDA receptor [72]. As a result, it has been postulated that antagonizing NMDA receptors may have antidepressant effects. This has been

investigated with the NMDA antagonist ketamine with promising results. In an initial proof-of-concept RCT, Berman *et al.* demonstrated that a single intravenous dose of ketamine (0.5 mg/kg) led to a rapid significant improvement in depressive symptoms [73]. The mood improvement peaked at 72 h post-ketamine treatment and was not due to the transient neurocognitive effects of ketamine (including the dissociative and psychotomimetic effects), since these did not last for more than 2 h. More recently, a RCT replicated the Berman *et al.* study by administering a single intravenous dose of ketamine (0.5 mg/kg) or placebo in 18 patients with treatment-resistant depression [74]. It was found in this trial that within hours of administering the active treatment, patients demonstrated a marked response that maintained for a week postinfusion. One of the important aspects of ketamine treatment is its effect on suicidal thoughts. Contrary to the effects of many antidepressants that have been suggested to possibly worsen suicidality, especially in adolescents and young adults [75], ketamine has been shown to rapidly improve suicidal ideation [76–78]. As such, ketamine may prove to be an important addition to current antidepressant treatment. The excitement related to the findings of ketamine in depression have been highlighted in various reports in popular publications, such as TIME magazine [79]. Further work is currently underway examining the effect of repeated ketamine administration and also the use of alternative glutaminergic drugs that can be given orally.

■ Substance P/NK1 antagonists

Substance P is a peptide neurotransmitter found within the CNS and which binds to NK1 receptors. NK1 receptor antagonists have been investigated for potential antidepressant efficacy for over a decade following positive preclinical signals and early proof-of-concept trails. It was proposed that these drugs may have direct effect on mood, independent of other neurotransmitter systems [80]. However, subsequent larger RCTs in MDD were rather disappointing, although interest continued in relation to their role in treating various anxiety disorders [81]. More recently casopitant, which is a selective NK1 antagonist that leads to high levels of receptor occupancy at doses being trialed, has been investigated by GlaxoSmithKline. In a recent paper, Ratti *et al.* presented two Phase II RCTs in patients with MDD [82]. Trial 1, compared the effect of an 8-week course of casopitant 30 or 80 mg, or placebo daily and found that the higher dose, but not the lower dose, led to a significant improvement on the HDRS scale compared with placebo with a 2.7 point difference. However, trial 2, which had an active comparator paroxetine (30 mg daily), found that neither casopitant (titrated up to 120 mg daily), nor paroxetine separated from placebo

on the HDRS scale. Whether or not the difficult in determining whether NK1 antagonists are antidepressants is due to the fundamental problems with RCTs in depression discussed above is not clear. It is also not clear if any potential effects are being mediated via an entirely novel mechanism. Recent evidence indicates that their action may be via interactions with pathways other than those related to substance P, including the hypothalamic–pituitary–adrenal axis, and 5-HT and NA neurotransmitter systems [83,84].

■ Neuroactive steroids & antiglucocorticoid treatments

Neuroactive steroids, whether produced *de novo* within the central nervous system (neurosteroids) or in the periphery are considered unique among steroids since they can alter neuronal excitability via effects on neurotransmitter receptors [85]. For example, neuroactive steroids have been shown to modulate inhibitory $GABA_A$ receptors and excitatory NMDA receptors. They have also been implicated in the pathophysiology of depression and as a potential target for the development of novel antidepressant treatments [86]. For example, decreased plasma levels of the neurosteroids $3\alpha,5\alpha$-tetrahydroprogesterone (allopregnanolone) and $3\alpha,5\beta$-tetrahydroprogesterone (pregnanolone) have been found in depressed patients (including those who are medication-naive) [87,88]. Other neurosteroids, namely dehydroepiandrosterone (DHEA) and its sulphated ester DHEA-S have been shown to inversely correlate with more depressed mood [89], although this is still controversial [90,91]. A more accurate and consistent 'functional' measure of corticosteroid levels in depression is the cortisol/DHEA ratio [92,93]. Indeed raised cortisol/DHEA ratio have been shown in depressed patients compared with controls in many [93–96], although not all [97], studies. Treatment with DHEA and pregnenolone have shown antidepressant-like effects in animal studies [98,99]. In humans, DHEA treatment has been shown to improve mood in depressed patients [100] as well as in healthy subjects [91]. The antidepressant effects of DHEA may relate to its functional antiglucocorticoid properties via correction of abnormally elevated cortisol/DHEA ratio. However, other mechanisms including direct effects of DHEA on 5-HT and GABA receptors have been postulated [101].

Depression is associated with significant abnormalities of the hypothalamic–pituitary–adrenal axis [10,102,103], particularly elevated corticosteroid concentrations (or cortisol/DHEA ratios). As a result, a large number of studies over the last few decades have explored a range of antiglucocorticoid treatments including administration of DHEA (described above), corticotrophin releasing hormone antagonists, glucocorticoid receptor

antagonists such as mifepristone, and steroid synthesis inhibitors such as metyrapone [104,105]. Most studies to date have essentially been small proof-of-concept trials and the results are somewhat mixed [104,106]. An exception to these are three RCTs of mifepristone in patients with psychotic MDD. The first was conducted in 221 patients randomized to mifepristone or placebo and found no significant effect of the drug on depressive symptoms, but did find a significant effect on psychotic symptoms measured using the Brief Psychiatric Rating Scale [107]. As a result in the second study in 258 patients, the primary outcome measure was response, defined as a 50% decrease in the Brief Psychiatric Rating Scale score [108]. There was no significant difference between mifepristone and placebo on the primary outcome; however, the authors noted that those with a mifepristone plasma concentration ≥1800 ng/ml were significantly more likely to respond. The third and most recent RCT examined mifepristone in 433 patients with psychotic MDD [109]. Again there was no significant difference between the drug and placebo on the primary outcome, although using an *a priori* plasma concentration cut off of 1660 ng/ml, those patients with higher levels were more likely to have a rapid and sustained improvement in symptoms compared with placebo. Clearly, the fact that all three of these RCTs failed on primary outcome measures suggest that the case is far from proven for a role of mifepristone in the management of psychotic depression.

Another area of current research is the use of the steroid synthesis inhibitor metyrapone as an augmentation agent with antidepressants in patients with treatment-refractory depression [105]. There are preclinical data that suggest the addition of metyrapone to classical antidepressants enhances effects in standard tests of antidepressant activity [110]. The main published clinical trial supporting this line of research currently is that of Jahn *et al.* who conducted a study in 63 patients with MDD, randomized to placebo or metyrapone added into standard antidepressant treatment with either nefazadone or fluvoxamine [111]. A significantly higher response rate was found in patients treated with metyrapone. There is currently a multicenter independently funded study being carried out in the UK investigating the efficacy of metyrapone augmentation of standard serotonergic antidepressants in patients with treatment refractory depression (The ADD Study [203]). Results are awaited.

Future perspective

While there has been contention over the efficacy of antidepressants for the treatment of MDD, the conclusion is most authorities argue that currently available drugs are effective and should continue to be used. It seems unlikely that the rate of prescribing will do anything other than continue to increase as it has been doing over the last couple of decades [112]. While guidelines have essentially raised the hurdle in terms of who to prescribe antidepressants to by switching from ICD-10 to DSM-IV criteria for depression [6,113], it is unclear that this is having much impact in primary care where most antidepressant prescribing occurs, certainly in the UK.

Recent large RCTs within the last 2 years have demonstrated the efficacy of the antidepressant agomelatine in MDD. This drug is of interest given its novel pharmacological mechanism of action. However, from a clinical stand point its main advantage over currently available drugs appears to be its high degree of tolerability. Whether there are clinically significant differences in efficacy between agomelatine and other antidepressants is difficult to say, at least in part due to the inherent problems in the current design and analysis of RCTs in depression. This uncertainty has been a factor in medicines management bodies especially in the UK, attempting to limit the use of agomelatine due to its higher purchase cost compared with generic anti-depressants. This is having the consequence of a much slower take up of the drug in the UK compared with other countries in Europe. Until the drug goes off patent, usage may only increase if there is clinical experience of benefits from its use.

The problems of determining differences in efficacy not just between antidepressants and placebo, but especially between different antidepressants also hinder the ability to definitively determine whether there is any advantage to the use of antidepressant combinations. It is of some concern that by far the largest study of combinations was conducted in a potentially somewhat unusual population of patients with MDD with very high rates of childhood abuse and early onset of depression. As a result, unless revisions of guidelines come out strongly against the use of combinations, they may continue to be employed by those clinicians that have faith in them.

The data regarding antipsychotic augmentation of antidepressants for patients with suboptimal response to monotherapy are very persuasive. In particular, there is strong evidence for the use of quetiapine, which is licensed in Europe and the USA, and aripiprazole, which is only licensed in the latter. The size of the data sets for both of these drugs exceeds that for the traditional gold standard for augmentation, lithium, certainly in terms of numbers of patients included in RCTs. Given the greater ease of use of antipsychotics compared with lithium, which requires blood monitoring, then it is likely that antipsychotics will continue to replace lithium as clinicians first-line choice as an augmentation agent.

In terms of new therapeutic options on the horizon, it is easy to be somewhat pessimistic given the withdrawal of a number of major pharmaceutical companies from neuroscience research in the last couple of years. In addition, there is the fundamental problem of conducting RCTs in patients with MDD, which makes detecting an effect of a novel drug challenging. This may well continue to be the case until there are major break throughs with regard to our understanding of the pathophysiology of depression. Most people would agree that the umbrella label of 'depression' probably covers a heterogeneous group of pathologies. Until this

Executive summary

Do antidepressants work in patients with major depressive disorder?
■ It has been suggested that antidepressants are only of clinical utility in patients with very severe depression, although the methodologies leading to this view have been criticized.
■ Mean differences in rating scale scores between patients treated with antidepressants versus placebo may obscure important differences. Analyzing response data using a bimodal distribution may be more clinically meaningful.
■ National guidelines continue to recommend the use of antidepressants in moderate to severe major depressive disorder (MDD).

Recent clinical trials of currently available treatments
■ Agomelatine
 - Agomelatine is a melatonergic agonist and $5-HT_{2C}$ antagonist with efficacy as an antidepressant.
 - It has a favorable side-effect profile compared with other antidepressants but routine liver function testing is required by the drug's authorization.
■ Antidepressant combinations
 - Combinations of antidepressants with complementary mechanisms of action are frequently used for patients with treatment refractory depression.
 - Studies examining the efficacy of such combinations show conflicting findings, perhaps due to differences in study design.
 - Guidelines currently recommend consideration of antidepressant combinations for refractory patients. It is unclear if this advice needs to change.
■ Antidepressant augmentation strategies
 - There are data supporting second-generation antipsychotic augmentation of antidepressants in patients with sub-optimal response, especially quetiapine and aripiprazole. Both are licensed for this use in the USA but only quetiapine is licensed in Europe.

Potential future pharmacotherapeutic options
■ Vortioxetine
 - Vortioxetine is a 'multimodal' antidepressant that acts as an agonist at $5-HT_{1A}$ and $5-HT_{1B}$ receptors and an antagonist at $5-HT_3$ and $5-HT_7$ receptors. It also is a 5-HT transporter inhibitor. It is under review for treatment of MDD.
■ Dopamine receptor ligands and 5-HT, noradrenalin, dopamine triple reuptake inhibitors
 - Dopaminergic dysregulation may be implicated in a number of depressive symptoms.
 - Triple reuptake inhibitors (5-HT, noradrenalin and dopamine reuptake inhibitors) have been under development, including amitifadine.
 - There are theoretical concerns that dopamine uptake blockade might lead to abuse potential. This has not been seen in one study addressing this.
■ Glutamate
 - A range of studies demonstrate glutaminergic dysfunction in MDD.
 - Intravenous ketamine (an NMDA receptor antagonist) has shown promising results. However its use may be limited by its mode of administration and dissociative side effects.
 - Alternative glutaminergic drugs are under investigation.
■ Substance P/NK1 antagonists
 - Substance P is a centrally active peptide acting on NK1 receptors.
 - Casopitant is a selective NK1 antagonist that is being trialed in MDD with some positive results.
■ Neuroactive steroids & antiglucocorticoid treatments
 - The neurosteroid dehydroepiandrosterone has shown antidepressant-like effects in animal studies and shown to improve mood in healthy volunteers and depressed patients.
 - Depression is associated with significant abnormalities of the hypothalamic–pituitary–adrenal axis.
 - Three randomized controlled trials have examined mifepristone (a glucocorticoid receptor antagonist) in patients with psychotic MDD. In all, the drug failed on the primary outcome measure, although effects were seen on secondary outcomes and when examining response in patients with higher plasma levels. Research into mifepristone continues.
 - Metyrapone, a steroid synthesis inhibitor, has also been studied as an augmentation agent in patients with treatment refractory depression and results of a large trial in the UK are awaited.

is better understood and clarified, it will not be possible to stratify patients and enable focused targeting of specific treatments to specific patients. These issues may be particularly relevant to the less than dramatic findings with various novel therapies, including the NK1 antagonists and the antiglucocorticoids. As a result, the only new treatments coming over the horizon that have a high chance of penetrating routine clinical practice are drugs such as vortioxetine and amitifadine, which continue to act via similar monoaminergic mechanisms to current antidepressants. Perhaps the one possible exception and bright light is ketamine and glutaminergic treatments. However, despite very positive findings over 6 years ago, it is still not at all clear if and when such drugs will enter routine clinical practice.

References

Papers of special note have been highlighted as:
- ■ of interest

1   Kennedy N, Paykel ES. Residual symptoms at remission from depression: impact on long-term outcome. *J. Affect. Disord.* 80(2–3), 135–144 (2004).

2   Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom Med.* 65(2), 201–210 (2003).

3   Thomson W. Lifting the shroud on depression and premature mortality: a 49-year follow-up study. *J. Affect. Disord.* 130(1–2), 60–65 (2011).

4   WHO. *The global burden of disease: 2004 update.* WHO Press, Geneva, Switzerland (2008).

5   Anderson IM, Ferrier IN, Baldwin RC *et al.* Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. *J. Psychopharmacol.* 22(4), 343–396 (2008).

■   **A good evidence-based and easily readable set of guidance for the management of depression. Due to be updated in 2013.**

6   NICE. Depression: the treatment and management of depression in adults (update). NICE clinical guidelines, 90 (2009).

7   Rush AJ, Trivedi MH, Wisniewski SR *et al.* Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am. J. Psychother.* 163(11), 1905–1917 (2006).

8   Hollinghurst S, Peters TJ, Gunnell D. Opportunity cost of antidepressant prescribing in England: analysis of routine data. *Br. Med. J.* 330(7498), 999–1000 (2005).

9   Kirsch I, Deacon BJ, Huedo-Medine TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the food and drug administration. *PLoS Med.* 5(2), 260–268 (2008).

■   **A much discussed paper due to the controversy it generated. The authors believe that the conclusions drawn are incorrect.**

10   McAllister-Williams RH. Do antidepressants work? A commentary on "Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration" by Kirsch *et al*. *Evid. Based Ment. Health* 11(3), 66–68 (2008).

11   Möller HJ. Isn't the efficacy of antidepressants clinically relevant? A critical comment on the results of the metaanalysis by Kirsch *et al*. 2008. *Eur. Arch. Psychiatry Clin. Neurosci.* 258(8), 451–455 (2008).

12   Fountoulakis KN, Möller HJ. Efficacy of antidepressants: a re-analysis and re-interpretation of the Kirsch data. *Int. J. Neuropsychopharmacol.* 14(3), 405–412 (2011).

13   Horder J, Matthews P, Waldmann R. Placebo, Prozac and PLoS: significant lessons for psychopharmacology. *J. Psychopharmacol.* 25(10), 1277–1288 (2011).

14   Vöhringer PA, Ghaemi SN. Solving the antidepressant efficacy question: effect sizes in major depressive disorder. *Clinical Therapeutics* 33(12), B49–B61 (2011).

15   Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N. Engl. J. Med.* 358(3), 252–260 (2008).

16   Huedo-Medina TB, Johnson BT, Kirsch I. Kirsch *et al.* calculations are correct: reconsidering Fountoulakis & Möller's re-analysis of the Kirsch data. *Int. J. Neuropsychopharmacol.* 15(8), 1193–1198 (2012).

17   Gibbons RD, Hur K, Brown CH, Davis JM, Mann JJ. Benefits from antidepressants: synthesis of 6-week patient-level outcomes from double-blind placebo-controlled randomized trials of fluoxetine and venlafaxine. *Arch. Gen. Psychiatry* 69(6), 572–579 (2012).

18   Melander H, Salmonson T, Abadie E, van Zwieten-Boot B. A regulatory Apologia – a review of placebo-controlled studies in regulatory submissions of new-generation antidepressants. *Eur. Neuropsychopharmacol.* 18(9), 623–627 (2008).

19   Hegerl U, Mergl R. The clinical significance of antidepressant treatment effects cannot be derived from placebo-verum response differences. *J. Psychopharmacol.* 24(4), 445–448 (2010).

20   Moncrieff J, Kirsch I. Efficacy of antidepressants in adults. *Br. Med. J.* 331(7509), 155–157 (2005).

21   Thase ME, Larsen KG, Kennedy SH. Assessing the 'true' effect of active antidepressant therapy v. placebo in major depressive disorder: use of a mixture model. *Br. J. Psychiatry* 199(6), 501–507 (2011).

■   **An interesting and novel analysis approach to antidepressant randomized controlled trials that may better ascertain the clinical significance (or otherwise) of treatments.**

22   Gueorguieva R, Mallinckrodt C, Krystal JH. Trajectories of depression severity in clinical trials of duloxetine: insights into antidepressant and placebo responses. *Arch. Gen. Psychiatry* 68(12), 1227–1237 (2011).

23   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. Pharmacol. Exp. Ther.* 306(3), 954–964 (2003).

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

25   Kennedy SH, Emsley R. Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. *Eur. Neuropsychopharmacol.* 16(2), 93–100 (2006).

26   Stahl SM, Fava M, Trivedi MH, Caputo A, Shah A, Post A. Agomelatine in the treatment of major depressive disorder: an 8-week, multicenter, randomized, placebo-controlled trial. *J. Clin. Psychiatry*, 71(5), 616–626 (2010).

27   Zajecka J, Schatzberg A, Stahl S, Shah A, Caputo A, Post A. Efficacy and safety of agomelatine in the treatment of major depressive disorder a multicenter, randomized, double-blind, placebo-controlled trial. *J. Clin. Psychopharmacol.* 30(2), 135–144 (2010).

28   Goodwin GM, Emsley R, Rembry S, Rouillon F. Agomelatine Study Group. Agomelatine prevents relapse in patients with major depressive disorder without evidence of a discontinuation syndrome: a 24-week randomized, double-blind, placebo-controlled trial. *J. Clin. Psychiatry* 70(8), 1128–1137 (2009).

29   Kennedy SH, Rizvi S, Fulton K, Rasmussen J. A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. *J. Clin. Psychopharmacol.* 28(3), 329–333 (2008).

30   Kasper S, Hajak G, Wulff K *et al.* Efficacy of the novel antidepressant agomelatine on the circadian rest-activity cycle and depressive and anxiety symptoms in patients with major depressive disorder: a randomized, double-blind comparison with sertraline. *J. Clin. Psychiatry* 71(2), 109–120 (2010).

31   Hale A, Corral RM, Mencacci C, Ruiz JS, Severo CA, Gentil V. Superior antidepressant efficacy results of agomelatine versus fluoxetine in severe MDD patients: a randomized,

double-blind study. *Int. Clin. Psychopharmacol.* 25(6), 305–314 (2010).

32   McAllister-Williams RH, Baldwin DS, Haddad PM, Bazire S. The use of antidepressants in clinical practice: focus on agomelatine. *Hum. Psychopharmacol.* 25(2), 95–102 (2010).

■   **A clinically useful review of agomelatine.**

33   Laux G. The antidepressant agomelatine in daily practice: results of the non-interventional study VIVALDI. *Pharmacopsychiatry* 45(7), 284–291 (2012).

34   Choi E, Zmarlicka M, Ehret MJ. Vilazodone: a novel antidepressant. *Am. J. Health Syst. Pharm.* 69(18), 1551–1557 (2012).

35   Goldberg RS, Thornton WE. Combined tricyclic MAOI therapy for refractory depression: a review, with guidelines for appropriate usage. *J. Clin. Pharmacol.* 18(2–3), 143–147 (1978).

36   Carpenter LL, Yasmin S, Price LH. A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. *Biol. Psychiatry* 51(2), 183–188 (2002).

37   McGrath PJ, Stewart JW, Fava M *et al.* Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. *Am. J. Psychother.* 163(9), 1531–1541 (2006).

38   Blier P, Gobbi G, Turcotte JE *et al.* Mirtazapine and paroxetine in major depression: a comparison of monotherapy versus their combination. *Eur. Neuropsychopharmacol.* 19, 457–465 (2009).

39   Blier P, Herbert C, Tremblay P, Laberge L, Hebert RN, Bergeron R. Combination of antidepressant medications from treatment initiation for major depressive disorder: a double-blind randomized study. *Am. J. Psychother.* 167, 281–288 (2010).

40   Rush AJ, Trivedi MH, Stewart JW *et al.* Combining medications to enhance depression outcomes (CO-MED): acute and long-term outcomes of a single-blind randomized study. *Am. J. Psychother.* 168(7), 689–701 (2011).

41   Bobo WV, Chen H, Trivedi MH *et al.* Randomized comparison of selective serotonin reuptake inhibitor (escitalopram) monotherapy and antidepressant combination pharmacotherapy for major depressive disorder with melancholic features: a CO-MED report. *J. Affect. Disord.* 133(3), 467–476 (2011).

42   Friedman ES, Davis LL, Zisook S *et al.* Baseline depression severity as a predictor of single and combination antidepressant treatment outcome: results from the CO-

MED trial. *Eur. Neuropsychopharmacol.* 22(3), 183–199 (2012).

43   Thase ME. Combined antidepressant strategies are not more effective than vigorous escitalopram monotherapy: results of the CO-MED study. *Curr. Psychiatry Rep.* 13(6), 434–436 (2011).

44   Coryell W. The search for improved antidepressant strategies: is bigger better? *Am. J. Psychiatry* 168(7), 664–666 (2011).

■   **A good commentary on antidepressant combination studies.**

45   Bauer M, Whybrow PC, Angst J *et al.* World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: acute and continuation treatment of major depressive disorder. *World J. Biol. Psychiatry*, 3(1), 5–43 (2002).

46   Lam RW, Kennedy SH, Grigoriadis S *et al.* Canadian network for mood and anxiety treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. III. Pharmacotherapy. *J. Affect. Disord.* 117(Suppl. 1), S26–S43 (2009).

47   Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. *Am. J. Psychother.* 166(9), 980–991 (2009).

■   **A good meta-analysis of atypical augmentation studies, though does not include the most recent data on quetiapine or aripiprazole.**

48   El-Khalili N, Joyce M, Atkinson S *et al.* Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in major depressive disorder (MDD) in patients with an inadequate response to ongoing antidepressant treatment: a multicentre, randomized, double-blind, placebo-controlled study. *Int. J. Neuropsychopharmacol.* 13(7), 917–932 (2010).

49   Bortnick B, El-Khalili N, Banov M *et al.* Efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) monotherapy in major depressive disorder: a placebo-controlled, randomized study. *J. Affect. Disord.* 128(1–2), 83–94 (2011).

50   Berman RM Marcus RN, Swanink R *et al.* 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(6), 843–853 (2007).

51   Marcus RN, McQuade RD, Carson WH *et al*. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J. Clin. Psychopharmacol.* 28(2), 156–165 (2008).

52   Berman RM, Fava M, Thase ME *et al*. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. *CNS Spectr.* 14(4), 197–206 (2009).

53   Reimherr FW, Martin ML, Eudicone JM *et al*. A pooled MADRS/IDS cross-correlation analysis: clinician and patient self-report assessment of improvement in core depressive symptoms with adjunctive aripiprazole. *J. Clin. Psychopharmacol.* 30(3), 300–305 (2010).

54   Bang-Andersen B, Ruhland T, Jørgensen M *et al*. Discovery of 1-[2-(2,4-Dimethylphenylsulfanyl)phenyl] piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. *J. Med. Chem.* 54(9), 3206–3221 (2011).

55   Alvarez E, Perez V, Dragheim M, Loft H, Artigas F. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. *Int. J. Neuropsychopharmacol.* 15(5), 589–600 (2012).

56   Mørk A, Pehrson A, Brennum LT *et al*. Pharmacological effects of Lu AA21004: a novel multimodal compound for the treatment of major depressive disorder. *J. Pharmacol. Exp. Ther.* 340(3), 666–675 (2012).

57   Baldwin DS, Loft H, Dragheim M. A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive disorder (MDD). *Eur. Neuropsychopharmacol.* 22(7), 482–491 (2012).

58   Katona C, Hansen T, Olsen CK. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *Int. Clin. Psychopharmacol.* 27(4), 215–223 (2012).

59   Papakostas GI, Thaseb ME, Fava M, Nelson JC, Shelton C. Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents. *Biol. Psychiatry* 62(11), 1217–1227 (2007).

60   Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. *Arch. Gen. Psychiatry* 64(3), 327–337 (2007).

61   Guiard BP, El Mansari M, Blier P. Prospect of a dopamine contribution in the next generation of antidepressant drugs: the triple reuptake inhibitors. *Curr. Drug Targets* 10(11), 1069–1084 (2009).

62   Blier P, Briley M. The noradrenergic symptom cluster: clinical expression and neuropharmacology. *Neuropsychiatr. Dis. Treat.* 7(Suppl.), 15–20 (2011).

63   Ascher JA, Cole JO, Colin JN *et al*. Bupropion: a review of its mechanism of antidepressant activity. *J. Clin. Psychiatry* 56(Suppl. 7), 395–401 (1995).

64   Fava M, Rush AJ, Thase ME *et al*. 15 years of clinical experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. *Prim. Care Companion J. Clin. Psychiatry* 7(3), 106–113 (2005).

65   Inoue T, Kitaichi Y, Masui T *et al*. Pramipexole for stage 2 treatment-resistant major depression: an open study. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 34(8), 1446–1449 (2010).

66   Tran P, Skolnick P, Czobor P *et al*. Efficacy and tolerability of the novel triple reuptake inhibitor amitifadine in the treatment of patients with major depressive disorder: a randomized, double-blind, placebo-controlled trial. *J. Psychiatr. Res.* 46(1), 64–71 (2012).

67   Schoedel KA *et al*. Subjective and objective effects of the novel triple reuptake inhibitor tesofensine in recreational stimulant users. *Clin Pharmacol Ther.* 88(1), 69–78 (2010).

68   Kim JS, Meier D, Chakraborty B, Manniche PM, Sellers EM. Increased serum glutamate in depressed patients. *Arch. Psychiatr. Nerven.* 232(4), 299–304 (1982).

69   Mitani H, Shirayama Y, Yamada T, Maeda K, Ashby CR Jr, Kawahara R. Correlation between plasma levels of glutamate, alanine and serine with severity of depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 30(6), 1155–1158 (2006).

70   Frye MA, Tsai GE, Huggins T, Coyle JT, Post RM. Low cerebrospinal fluid glutamate and glycine in refractory affective disorder. *Biol. Psychiatry* 61(2), 162–166 (2007).

71   Luykx JJ, Laban KG, van den Heuvel MP *et al*. Region and state specific glutamate downregulation in major depressive disorder: a meta-analysis of 1H-MRS findings. *Neurosci. Biobehav. Rev.* 36(1), 198–205 (2012).

72   Bobula B, Hess G. Antidepressant treatments-induced modifications of glutamatergic transmission in rat frontal cortex. *Pharmacol. Rep.* 60(6), 865–871 (2008).

73   Berman RM, Cappiello A, Anand A *et al*. Antidepressant effects of ketamine in depressed patients. *Biol. Psychiatry* 47(4), 351–354 (2000).

74   Zarate CA Jr, Singh JB, Carlson PJ *et al*. A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch. Gen. Psychiatry* 63(8), 856–864 (2006).

▪   **An important proof-of-concept study with intravenous ketamine in major depressive disorders.**

75   Carpenter DJ, Fong R, Kraus JE, Davies JT, Moore C, Thase ME. Meta-analysis of efficacy and treatment-emergent suicidality in adults by psychiatric indication and age subgroup following initiation of paroxetine therapy: a complete set of randomized placebo-controlled trials. *J. Clin. Psychiatry* 72(11), 1503–1514 (2011).

76   Price RB, Nock MK, Charney DS, Mathew SJ. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol. Psychiatry* 66(5), 522–526 (2009).

77   DiazGranados N, Ibrahim LA, Brutsche NE *et al*. Rapid resolution of suicidal ideation after a single infusion of an *N*-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J. Clin. Psychiatry* 71(12), 1605–1611 (2010).

78   Larkin GL, Beautrais AL. A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. *Int. J. Neuropsychopharmacol.* 14(8), 1127–1131 (2011).

79   Szalavitz M. *Ketamine for depression: the most important advance in field in 50 years?* TIME, 5 October 2012.

80   Kramer MS, Cutler N, Feighner J *et al*. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science* 281(5383), 1640–1645 (1998).

81   Hafizi S, Chandra P, Cowen PJ. Neurokinin-1 receptor antagonists as novel antidepressants: trials and tribulations. *Br. J. Psychiatry* 191, 282–284 (2007).

82   Ratti E, Bellew K, Bettica P *et al*. Results from 2 randomized, double-blind, placebo-controlled studies of the novel nk1 receptor antagonist casopitant in patients with major depressive disorder. *J. Clin. Psychopharmacol.* 31(6), 727–733 (2011).

83   Gobbi G, Blier P. Effect of neurokinin-1 receptor antagonists on serotoninergic, noradrenergic and hippocampal neurons: comparison with antidepressant drugs. *Peptides* 26(8), 1383–1393 (2005).

84   Griebel G, Holsboer F. Neuropeptide receptor ligands as drugs for psychiatric diseases: the end of the beginning? *Nat. Rev. Drug Discov.* 11(6), 462–478 (2012).

85   Rupprecht R, Holsboer F. Neuroactive steroids: mechanisms of action and neuropsychopharmacological perspectives. *Trends Neurosci.* 22(9), 410–416 (1999).

86   Schüle C, Eser D, Baghai TC, Nothdurfter C, Kessler JS, Rupprecht R. Neuroactive steroids in affective disorders: target for novel antidepressant or anxiolytic drugs? *Neuroscience* 191, 55–77 (2011).

87   George MS, Guidotti A, Rubinow D, Pan B, Mikalauskas K, Post RM. CSF neuroactive steroids in affective disorders: pregnenolone, progesterone, and DBI. *Biol. Psychiatry* 35(10), 775–780 (1994).

88   Romeo E, Ströhle A, Spalletta G *et al.* Effects of antidepressant treatment on neuroactive steroids in major depression. *Am. J. Psychother.* 155(7), 910–913 (1998).

89   Barrett-Connor E, von Mühlen D, Laughlin GA, Kripke A. Endogenous levels of dehydroepiandrosterone sulfate, but not other sex hormones, are associated with depressed mood in older women: the rancho bernardo study. *J. Am. Soc. Geriatr. Dent.* 47(6), 685–691 (1999).

90   Heuser I, Deuschle M, Luppa P, Schweiger U, Standhardt H, Weber B. Increased diurnal plasma concentrations of dehydroepiandrosterone in depressed patients. *J. Clin. Endocrinol. Metab.* 83(9), 3130–3133 (1998).

91   Alhaj HA, Massey AE, McAllister-Williams RH. Effects of DHEA administration on episodic memory, cortisol and mood in healthy young men: a double-blind, placebo-controlled study. *Psychopharmacology* 188(4), 541–551 (2006).

92   Goodyer IM, Herbert J, Altham PME. Adrenal steroid secretion and major depression in 8- to 16-year-olds, III. Influence of cortisol/DHEA ratio at presentation on subsequent rates of disappointing life events and persistent major depression. *Psychol. Med.* 28(2), 265–273 (1998).

93   Young AH, Gallagher P, Porter RJ. Elevation of the cortisol-dehydroepiandrosterone ratio in drug-free depressed patients. *Am. J. Psychother.* 159(7), 1237–1239 (2002).

94   Michael A, Jenaway A, Paykel ES, Herbert J. Altered salivary dehydroepiandrosterone levels in major depression in adults. *Biol. Psychiatry* 48(10), 989–995 (2000).

95   Goodyer IM, Herbert J, Tamplin A. Psychoendocrine antecedents of persistent first-episode major depression in adolescents: a community-based longitudinal enquiry. *Psychol. Med.* 33(4), 601–610 (2003).

96   Markopoulou K, Papadopoulos A, Juruena MF, Poon L, Pariante CM, Cleare AJ. The ratio of cortisol/DHEA in treatment resistant depression. *Psychoneuroendocrinology* 34(1), 19–26 (2009).

97   Fabian TJ, Dew MA, Pollock BG *et al.* Endogenous concentrations of DHEA and DHEA-S decrease with remission of depression in older adults. *Biol. Psychiatry* 50(10), 767–774 (2001).

98   Reddy DS, Kaur G, Kulkarni SK. Sigma (σ 1) receptor mediated antidepressant-like effects of neurosteroids in the Porsolt forced swim test. *NeuroReport* 9(13), 3069–3073 (1998).

99   Urani A, Roman FJ, Phan VL, Su TP, Maurice T. The antidepressant-like effect induced by σ1-receptor agonists and neuroactive steroids in mice submitted to the forced swimming test. *J. Pharmacol. Exp. Ther.* 298(3), 1269–1279 (2001).

100 Wolkowitz OM, Reus VI, Keebler A *et al.* Double-blind treatment of major depression with dehydroepiandrosterone. *Am. J. Psychother.* 156(4), 646–649 (1999).

101 Bovenberg SA, van Uum SH, Hermus AR. Hermus, dehydroepiandrosterone administration in humans: evidence based? *Netherlands J. Med.* 63(8), 300–304 (2005).

102 Zunszain PA, Anacker C, Cattaneo A, Carvalho LA, Pariante CM. Glucocorticoids, cytokines and brain abnormalities in depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 35(3), 722–729 (2011).

103 O'Keane V, Frodl T, Dinan TG. A review of atypical depression in relation to the course of depression and changes in HPA axis organization. *Psychoneuroendocrinology* 37(10), 1589–1599 (2012).

104 Schüle C, Baghai TC, Eser D, Rupprecht R. Hypothalamic-pituitary-adrenocortical system dysregulation and new treatment strategies in depression. *Expert Rev. Neurother.* 9(7), 1005–1019 (2009).

105 Sigalas PD, Garg H, Watson S, McAllister-Williams RH, Ferrier IN. Metyrapone in treatment-resistant depression. *Ther. Adv. Psychopharmacology* 2(4), 139–149 (2012).

106 Gallagher P, Malik N, Newham J, Young AH, Ferrier IN, Mackin P. Antiglucocorticoid treatments for mood disorders. *Cochrane Database Syst. Rev.* 23(1), CD005168 (2008).

■   **A review of antiglucocorticoid treatments in mood disorders.**

107 DeBattista C, Belanoff J, Glass S. Mifepristone versus placebo in the treatment of psychosis in patients with psychotic major depression. *Biol. Psychiatry* 60(12), 1343–1349 (2006).

108 Blasey CM, Debattista C, Roe R, Block T, Belanoff JK. A multisite trial of mifepristone for the treatment of psychotic depression: a site-by-treatment interaction. *Contemp. Clin. Trials* 30(4), 284–288 (2009).

109 Blasey CM, Blasey CM, Block TS, Belanoff JK, Roe RL. Efficacy and safety of mifepristone for the treatment of psychotic depression. *J. Clin. Psychopharmacol.* 31(4), 436–440 (2011).

110 Rogóz Z. Potentiation of the antidepressant-like effect of desipramine or reboxetine by metyrapone in the forced swimming test in rats. *Pharmacol. Rep.* 61(6), 1173–1178 (2009).

111 Jahn H, Schick M, Kiefer F, Kellner M, Yassouridis A, Wiedemann K. Metyrapone as additive treatment in major depression: a double-blind and placebo-controlled trial. *Arch. Gen. Psychiatry* 61(12), 1235–1244 (2004).

112 Middleton N, Gunnell D, Whitley E, Dorling D, Frankel S. Secular trends in antidepressant prescribing in the UK, 1975–1998. *J. Public Health Med.* 23(4), 262–267 (2001).

113 NICE. Depression: management of depression in primary and secondary care – NICE guidance (2004).

■ **Websites**

201 Cochrane handbook for systematic reviews of interventions.
www.cochrane-handbook.org

202 European Medicines Agency. Withdrawn applications – Abilify.
www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000471/wapp/post-authorisation/human_wapp_000004.jsp&mid=WC0b01ac058001d128

203 Antiglucocorticoid augmentation of antidepressants in depression.
www.theADDStudy.co.uk