International Journal of Neuropsychopharmacology (2013), **16**, 1433–1442. © CINP 2013
doi:10.1017/S1461145712001605

REVIEW

Multi-modality: a new approach for the treatment of major depressive disorder

Elliott Richelson

Departments of Psychiatry and Pharmacology, Mayo Clinic, Jacksonville, FL, USA

Abstract

Effective treatment with antidepressants is currently limited by factors that affect treatment compliance, including delay in onset of therapeutic effects and intolerable side-effects. Recent data suggest that use of antidepressant combinations with different mechanisms of action may be a better first-line strategy prior to augmentation with other drug classes. The rationale for this approach is that combining multiple pharmacological actions affecting multiple monoamine targets produces greater efficacy. Several new multi-modal compounds are in development and early results for the most advanced agents indicate shorter onset of therapeutic effects and improved tolerability. By modulating multiple receptors and transmitter systems, it is hoped that these new agents may also treat some of the associated symptoms of major depressive disorder, such as anxiety and cognitive dysfunction.

Received 23 July 2012; Reviewed 10 August 2012; Revised 14 November 2012; Accepted 4 December 2012; First published online 30 January 2013

Key words: Antidepressant, brexpiprazole, MDD, multi-modal therapy, vilazodone, vortioxetine.

Unmet needs in major depressive disorder

Major depressive disorder (MDD) is often recurrent, with impact throughout the entire lifespan of the patient. It is associated with substantial general medical and psychiatric co-morbidities (Rush, 2007), has a significant effect on the psychosocial well-being of the patient, reduces productivity in the workplace or at school and has a substantial economic burden on the healthcare system (Ustun et al., 2004; Langlieb and Guico-Pabia, 2010). Treatment with antidepressants is indicated in MDD and this treatment is currently limited by factors that affect patient compliance, including delay in onset of therapeutic effects, intolerable side-effects (especially sexual dysfunction and weight gain), and other safety concerns. Further, the non-response rate to adequate first-line treatment with a single antidepressant is high; more than half of the patients in the National Institute of Mental Health's Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial were considered 'nonresponsive' to first-line treatment with a selective serotonin reuptake inhibitor (SSRI; Trivedi et al., 2006). In this large national study, the participants who responded and/or remitted in level 1 took an average of nearly 6 wk treatment to improve enough to reach a 'response' and almost 7 wk treatment to achieve 'remission' of depressive symptoms. Residual symptoms, such as anhedonia, fatigue and sleep problems, are also common in patients otherwise considered to be in remission. A study of patients who achieved 'remission' in the STAR*D trial found that the majority ($>90\%$) had ≥ 1 residual depressive symptom (median $=3$; Nierenberg et al., 2010).

Despite these issues, medication compliance is critical, because long-term treatment of MDD decreases the likelihood of relapse by as much as 70% (Rush et al., 2006). However, medication adherence among patients with MDD is disturbingly low, particularly in the long term (Ashton et al., 2005). Therefore, even with the availability of many efficacious treatments, psychiatrists and physicians in other specialties continue to be challenged by the task of effectively managing MDD. For these reasons, the therapeutic needs in MDD treatment include improved antidepressant selection for individual patient needs and improved overall effectiveness, safety and tolerability. One approach is to develop antidepressants with novel mechanisms of action that may provide faster onset of therapeutic effects, higher remission rates and improved tolerability. Additionally, treatment non-responders may respond to an antidepressant with a novel action.

Overview of current pharmacotherapy

Pharmacotherapy for MDD has been available since the introduction of tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs) in the 1950s. The first SSRIs were introduced in the 1980s and, due to their improved safety and tolerability profiles relative to TCAs and MAOIs (Rosenzweig-Lipson et al., 2007), they

Address for correspondence: Dr E. Richelson, Mayo Clinic Florida, 4500 San Pablo Road, Jacksonville, FL 32224, USA.
Tel.: 904 953 2439 *Fax*: 904 953 7117
Email: richel@mayo.edu

became the most widely prescribed medications for treating depression and related disorders (Bauer et al., 2008). The serotonin and norepinephrine (NE) reuptake inhibitors (SNRIs) venlafaxine, duloxetine and desvenlafaxine, as well as the SSRIs sertraline, paroxetine, citalopram and the stereoselective escitalopram, have been marketed since the early 1990s.

Only half to three-quarters of patients show a clinical response ($\geq$50% reduction in intensity of depressive symptoms) with their first trial of antidepressant medication (Rush et al., 2006; Trivedi et al., 2006). Thus, it is obvious that many patients are left with only a partial response or no improvement in symptoms. Clinicians traditionally use various strategies when a patient does not respond to initial treatment: reviewing the diagnosis; increasing the dose of antidepressant; switching to another antidepressant; augmenting an antidepressant with medications from other drug groups. The current standard of care is drug substitution, with or without a discontinuation period. However, because an antidepressant drug trial should last at least 6 wk, two consecutive attempts using different medications would require about 3 months. Similarly, the strategy of adding a second medication to an ongoing antidepressant regimen requires completion of a first trial, thereby still delaying response or remission in most patients. This delay is significant because about half of all patients stop taking their antidepressants within the first few months (Bull et al., 2002). It is clear that initial treatment decisions are critical to achieving remission.

Combination therapy ('polypharmacy') has traditionally been discouraged in psychiatry because of the increased risk of drug interactions and toxicity. However, combining an antidepressant with another antidepressant having a different mechanism of action has been an approach to treatment-resistant depression (TRD) after failure of all other strategies (Cascade et al., 2007). Using combination antidepressants when the only options were TCAs and MAOIs is rightly recognized as extremely risky. Also risky has been the combination of TCAs with SSRIs (particularly paroxetine and fluoxetine) that might inhibit the metabolism of the TCA, leading to toxic levels of the tricyclic drug (Alderman et al., 1997). Nonetheless, with the availability of better-tolerated antidepressants, use of antidepressant combinations has become more common (Mojtabai and Olfson, 2010).

Combining antidepressant medications

Use of antidepressant combinations with different mechanisms of action may be a better strategy prior to augmentation with drugs of other classes (Dodd et al., 2005; Stahl, 2010). The rationale for this approach is that combining multiple pharmacological actions affecting multiple monoamine targets produces greater efficacy. Many of the newer and more effective antidepressants already combine multiple mechanisms of action. For example, the SNRIs combine both serotonergic and noradrenergic (and cortical dopaminergic) actions; bupropion (a NE-dopamine reuptake inhibitor; NDRI) combines both noradrenergic and (weak) dopaminergic actions; mirtazapine combines α_2-adrenoceptor antagonism with antagonism of 5-HT_{2C}, 5-HT_{2A} and histamine H_1 receptors.

Although the results of individual trials comparing SNRIs with SSRIs in MDD can conflict (some showing equivalency and some showing superiority), meta-analyses of these trials suggest that SNRIs have a modest efficacy advantage and a slightly faster onset of antidepressant action, but with potentially lower tolerability (Papakostas et al., 2007). Recently published studies have also shown a more frequent early marked response in subjects treated with nortriptyline *vs.* citalopram (Uher et al., 2011), and greater percentages of response with mirtazapine *vs.* SSRIs (Thase et al., 2010).

Taking this idea a step further, a wealth of anecdotal evidence now indicates that combining antidepressant treatment may be an effective strategy in MDD. However, few randomized controlled trials have evaluated the combination approach and the results are inconsistent. In one of the earliest studies, Maes et al. examined whether combining the 5-HT_{1A} receptor antagonist pindolol or the 5-$HT_{2A/C}$ and α_2-adrenoceptor antagonist mianserin with the SSRI fluoxetine augments the clinical efficacy of antidepressive activity in the treatment of MDD and TRD. The results of this small (n=31) study showed that treatment with fluoxetine + pindolol or with fluoxetine + mianserin was significantly more effective than fluoxetine alone (Maes et al., 1999). In a small (n=39) proof-of-concept study, Nelson et al. showed that combining fluoxetine with the NE reuptake inhibitor, desipramine in non-treatment-resistant in-patients with a major depressive episode was significantly more likely to result in remission than was fluoxetine alone or desipramine alone (Nelson et al., 2004).

More recently, Blier et al. reported that combining mirtazapine with paroxetine provided a significantly greater decrease in Montgomery–Åsberg Depression Rating Scale (MADRS) scores in comparison with the monotherapy at days 28, 35 and 42, with a 10-point difference favouring combination therapy at day 42 (Blier et al., 2009). Following the initial favourable result, Blier and colleagues examined whether treatment with different combinations of antidepressant drugs was more effective than fluoxetine monotherapy. Compared to fluoxetine monotherapy, all three combination groups had significantly greater improvements on the Hamilton Depression Rating Scale (HAMD) and better remission rates. Interestingly, among patients who had a marked response, double-blind discontinuation of one agent produced relapse in about 40% of cases (Blier et al., 2010). In contrast, the most recently reported large (n=665) CO-MED single-blinded study by Rush et al. failed to show superiority in achieving acute and long-term

remission for antidepressant medication combinations *vs.* SSRI monotherapy (Rush et al., 2011). In their study, patients with at least moderately severe non-psychotic chronic and/or recurrent MDD were randomized to receive escitalopram (up to 20 mg/d) plus placebo, sustained-release bupropion (up to 400 mg/d) plus escitalopram (up to 20 mg/d) or extended-release venlafaxine (up to 300 mg/d) plus mirtazapine (up to 45 mg/d). Remission rates, response rates and most secondary outcomes did not differ among the treatment groups at 12 wk and the combination of extended-release venlafaxine plus mirtazapine may be associated with a greater risk of adverse events (Rush et al., 2011). In their conclusions, the CO-MED authors note that the lack of superiority of the combined antidepressants over monotherapy may be explained by the use of lower doses: 'which may not have been sufficient to realize the full potential value of combination antidepressant medications' (Rush et al., 2011). It must be noted that, because of the scant nature of prospective data comparing combined treatments *vs.* monotherapy, only limited conclusions can be drawn. Nevertheless, these data indicate potential new avenues for treatment that deserve further investigation.

Combining multiple pharmacological actions into one antidepressant

A major difficulty with regard to combining two antidepressants is ensuring that both are well tolerated when given together. This means starting one treatment and, if well tolerated, adding the second later. This issue would be overcome if a single agent could combine the necessary modes of action. Recently, the term 'multi-modal' was coined for compounds that contain at least two separate pharmacological modes of action that complement each other in terms of efficacy or tolerability (Nutt, 2009; Chang and Fava, 2010).

Almost all drugs have more than one known pharmacological mode of action, especially at supratherapeutic doses. However, in the majority of cases, the 'extra' mechanisms are unwanted and a potential cause of undesirable side-effects rather than a property that provides additional efficacy. When an undesired pharmacological action occurs at therapeutic doses, it is not considered a multi-modal drug, but rather a 'dirty' drug. Two or more therapeutic actions are what make a drug multi-modal rather than dirty. According to these definitions, the TCAs, which have many known pharmacological actions in addition to blocking the NE transporter (NET) and/or the serotonin transporter (SERT), are both multi-modal and dirty and are therefore not well tolerated. However, SNRIs are considered multi-modal because they retain the NET and SERT inhibitory properties of TCAs, but not the anticholinergic, anti-adrenergic or anti-histaminic properties.

The pharmacological rationale for multi-modal drugs in the treatment of MDD is clear. First, there is no single cause of MDD and a number of factors are thought to affect mood and trigger affective disorders. Second, numerous neural networks and, hence neurotransmitter pathways, have been implicated in the development of MDD (Maletic et al., 2007; Drevets et al., 2008). These networks involve the medial prefrontal cortex and closely related areas in the medial and caudolateral orbital cortex (medial prefrontal network), amygdala, hippocampus and ventromedial parts of the basal ganglia. In addition, serotonergic, noradrenergic, dopaminergic, GABAergic and glutamatergic pathways have all been implicated in the development of depression (Maletic et al., 2007). As such, treatment strategies with a broad influence on corticolimbic circuits implicated in depression are more likely than highly selective agents to be effective in the majority of patients (Maletic et al., 2007). Third, patients with MDD often suffer a wide range of associated symptoms such as anxiety and cognitive dysfunction. Agents with complementary components of action have a greater chance of controlling both the mood disturbances of depression and other associated symptoms (Millan, 2009). Finally, a wealth of evidence has shown that augmenting SSRIs with agents of other classes (including lithium salts, atypical antipsychotics, buspirone and thyroxine) enhances the therapeutic efficacy of SSRIs (Fava, 2009; Nelson, 2009; Thase, 2009). These improved effects are more than would be expected with dose increases and likely reflect the recruitment of mechanisms complementary to 5-HT reuptake inhibition (Millan, 2009).

Multi-modal drugs in development for MDD

For many years, MDD research has focused on developing superior pharmacotherapeutic strategies for the treatment of depression and there has been much interest in developing agents with multi-modal action. Such agents can be classified into three main types (Millan, 2009): (1) those that exclusively target monoaminergic neurocircuitry; (2) those that act at non-monoaminergic targets; (3) those with a monoaminergic mechanism that also affects non-monoaminergic pathways to enhance the clinical efficacy and/or tolerability of the antidepressant. All currently available agents target monoaminergic circuitry but have not clearly demonstrated improved efficacy *vs.* the older antidepressants (Montgomery et al., 2007; Papakostas et al., 2007).

Although our understanding of the neurocircuitry of depression is evolving and becoming more complex, the role of serotoninergic deficiency in the development of depression is generally accepted and well supported by the significant clinical effects exerted by SSRIs. Due to its widespread distribution in the brain and the paracrine manner in which serotonin is released, the serotoninergic system also interacts with the other neurotransmitter systems in the brain, thereby allowing serotonergic agents the potential to target non-monoaminergic mechanisms in MDD.

Table 1. Receptor profiles for the new multi-modal antidepressants compared with commonly used SSRIs and SNRIs[a,b]

	Drug	5-HT_{1A}	5-HT_{1B}	5-HT_{2C}	5-HT_3	5-HT_7	SERT inhibition	NET inhibition	DAT inhibition	α_1-adrenergic
SSRI	Citalopram (Airaksinen et al., 2004)						+++			
	Fluoxetine (Porter et al., 2003; Mondal et al., 2007)			++			+++	++		
SNRI	Duloxetine (Fava et al., 2006)						+++	+++	+	
	Venlafaxine (Herrera- Guzman et al., 2010)						+++	++		
Multi-modal	Vilazodone (Laughren et al., 2011)	+++					+++			
	Vortioxetine (Artigas et al., 1996)	+++	+++		+++	+++	+++			++
	Amitifadine/DOV 216,303						+++	+++	+++	

SSRI, serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; SERT, serotonin transporter; NET, norepinephrine transporter; DAT, dopamine transporter; +, weak affinity, ++, moderate affinity; +++, strong affinity.

[a] Based on data from Artigas et al. (1996), Porter et al. (2003), Airaksinen et al. (2004), Fava et al. (2006), Mondal et al. (2007), Herrera-Guzman et al. (2010) and Laughren et al. (2011).

[b] Due to the lack of data, brexpiprazole (OPC-34712) is not presented.

Many antidepressants for MDD are in clinical development or recently approved. Of these, there are currently four agents with a potential multi-modal action – vilazodone, vortioxetine (Lu AA21004), OPC-34712 and amitifadine (DOV 21,947)/DOV-216,303 – that have data available (Chancellor, 2011). Agomelatine is not considered in this review since its failure to reach the US market. Table 1 presents some qualitative data for the receptor and transporter affinities of these compounds compared to other marketed antidepressants.

Vilazodone

Vilazodone is a new antidepressant approved by the US Food and Drug Administration (FDA; January 2011) for the treatment of MDD. Its mechanism of action combines inhibition of serotonin reuptake and partial agonism of 5-HT_{1A} receptors. However, as with all antidepressants, the full mechanisms remain unclear (Dawson and Watson, 2009). The premise for its development was to shorten the onset of antidepressant action by blocking presynaptic 5-HT_{1A} autoreceptors, which initially act to inhibit serotonergic cell firing and 5-HT release (Dawson and Watson, 2009; Khan, 2009). Clinical studies have indeed reported that 40 mg/d vilazodone provides an antidepressant response (improved MADRS and HAMD-17 scores; $p<0.05$) after 1 wk treatment (Rickels et al., 2009) and a significantly higher response rate than placebo at week 8 (MADRS: treatment effect -3.6 *vs.* placebo $p=0.007$; Laughren et al., 2011). However, in a recent review, authors from the FDA noted that, while the results from the phase 3 trials were enough to satisfy them of vilazodone's efficacy over 8 wk, the trials were not adequately designed to show an early onset of action and – moreover – the statistically significant effect *vs.* placebo at 1 wk reported in one study was not replicated in other studies (Laughren et al., 2011).

As well as improving the onset of action of SSRIs, 5-HT_{1A} agents may also have direct therapeutic actions. For example, various 5-HT_{1A} partial agonists are reported to have antidepressant (Robinson et al., 1990), anti-anxiety (Schreiber and De Vry, 19 93) and anti-aggressive (de Boer and Koolhaas, 2005) properties. However, the clinical relevance of any of these reported actions remains to be clarified. 5-HT_{1A} receptor partial agonism has also been suggested to help resolve the sexual dysfunction side-effects associated with SERT inhibition (Landén et al., 1999; Dawson and Watson 2009).

At a dose of 40 mg/d, vilazodone is considered to have a tolerability profile similar to that observed with SSRIs; reported treatment-emergent adverse events with vilazodone include diarrhoea, nausea and somnolence (Laughren et al., 2011). Importantly, the presence of gastrointestinal side-effects causes the need for slower titration of vilazodone starting at lower than the maintenance dosing for at least 2 wk, thus potentially negating

the benefits of any 'rapid onset' effect (Singh and Schwartz, 2012).

Vortioxetine

Vortioxetine is also a partial agonist at the 5-HT_{1A} receptor as well as a blocker of the SERT, 5-HT_3 and 5-HT_7 receptors (Bang-Andersen et al., 2011). In this case, SERT inhibition is important for antidepressant and anxiolytic activity and the simultaneous use of an efficacious 5-HT_{1A} receptor agonist with a SERT inhibitor is predicted to desensitize rapidly the inhibitory somatodendritic 5-HT_{1A} autoreceptors and, at the same time, to mediate part of the antidepressant effect through activation of post-synaptic 5-HT_{1A} receptors (Artigas et al., 1996). Interestingly, at the studied dose of 5 mg, vortioxetine is reported to provide only approximately 40% SERT occupancy (Alvarez et al., 2011), although it has been estimated that therapeutic doses of SSRIs provided 80% SERT occupancy (Meyer, 2007).

In preclinical studies comparing vortioxetine with fluoxetine, vortioxetine produced a markedly faster recovery of 5-HT neuronal firing. This effect was partly due to the 5-HT_3 receptor antagonism of vortioxetine. 5-HT_3 receptors are the only ligand-gated ion channel of the serotonin receptor family and are localized in several areas involved in mood regulation. Vomiting reflex and mood are associated putative effects (Bétry et al., 2012). In addition, vortioxetine has antagonistic effects on 5-HT_7 receptors associated with sleep, circadian rhythm and mood.

In a recent randomized, controlled trial conducted in 429 patients with severe MDD (MADRS $\geq$30), treatment with 5 or 10 mg vortioxetine resulted in significant improvements *vs.* placebo in mean change from baseline in MADRS total score at week 6 ($p<0.0001$) and in nine of the 10 MADRS items. The treatment difference *vs.* placebo was similar to that seen in a control group of subjects given 225 mg venlafaxine (5 mg vortioxetine, 5.9 points; 10 mg, 5.7 points; venlafaxine, 6.4 points; Alvarez et al., 2011). This treatment difference for vortioxetine translates into a clinically relevant difference in response rates of between 22 and 32% (Melander et al., 2008). Importantly, significant improvements *vs.* placebo in HAMD-24 scores were observed for both doses of vortioxetine from the first visit (week 1) and for venlafaxine from the second week (Alvarez et al., 2011). The analysis of discontinuation rates due to adverse events in patients treated with vortioxetine also indicated a better tolerability profile compared with that of 225 mg venlafaxine (5 mg vortioxetine, 3%, 10 mg, 7%; venlafaxine, 14% discontinued due to adverse events; Alvarez et al., 2011).

These encouraging results are balanced by another 8-wk study comparing the efficacy of vortioxetine *vs.* placebo in patients with MDD and using duloxetine as active reference. At study end, the treatment effects of −1.7 (5-mg dose), −1.5 (10-mg dose), −1.4 (2.5-mg dose) were not found to be statistically significant *vs.* placebo. The effects of 60 mg duloxetine (−2.0 points) were also found to be not significant *vs.* placebo. However, most secondary end-points were supportive of likely efficacy for 5 and 10 mg vortioxetine and 60 mg duloxetine (Baldwin et al., 2012). Such 'negative findings' are common in MDD clinical studies. A recent analysis of randomized, controlled trials of antidepressants, normally considered efficacious for MDD, found only half (53%) of trials submitted to the FDA have been positive (Khin et al., 2011).

Brexpiprazole

Brexpiprazole, or OPC-34712, is a novel compound currently in development for MDD. It is a close structural analogue of aripiprazole and shares some of its pharmacological properties. As for aripiprazole, which is FDA approved as adjunct therapy for MDD, brexpiprazole is also being developed as adjunct therapy. According to its developers (Otsuka and Lundbeck), it has: 'broad activity across multiple monoamine systems and exhibits reduced partial agonist activity at D_2 dopamine receptors and enhanced affinity for specific serotonin receptors (e.g. 5-HT_{1A}, 5-HT_{2A} and 5-HT_7)'. Phase 2 clinical trial results for brexpiprazole as an adjunct to other antidepressants have been presented in abstract form only (Otsuka Ltd, 2011). In patients who were proven to have an inadequate response to antidepressants (one of the following: desvenlafaxine; escitalopram; fluoxetine; paroxetine; sertraline; venlafaxine) within the same episode, adjunctive treatment with brexpiprazole (1.5 mg) significantly improved mean MADRS total score, from baseline to end-point *vs.* placebo. Although at this stage no conclusions can be drawn, we eagerly await the full publication of results and results of other trials listed on clinicaltrials.gov.

Amitifadine (*DOV 21,947*)/*DOV-216,303*

Amitifadine (previously DOV 21,947) and DOV 216,303 (a racemic mixture of which amitifadine is one of the enantiomers) are both currently in development for MDD. They are in the class of so-called triple reuptake inhibitors or serotonin-NE-dopamine reuptake inhibitor, which inhibit the reuptake of NE, serotonin and dopamine (i.e. the three neurotransmitters most closely linked to MDD; Liang and Richelson, 2008). Of this potentially new drug class, amitifadine and DOV 216,303 are the most advanced in development and are currently the only ones to show clinical efficacy in MDD. Trials with other triple reuptake inhibitors – SEP225289 (Sepracor Inc., 2009) and GSK372475 (Learned et al., 2012) – have not been successful and have led to much questioning of whether triples are actually efficacious in MDD.

According to its developer, amitifadine is a serotonin-preferring triple reuptake inhibitor with lower affinity for dopamine transporters. This is different from the failed

candidates SEP225289, which has higher affinity at the dopamine transporter (DeLorenzo et al., 2011), and GSK372475, which has similar potency at all three transporters (Learned et al., 2012). Such differences in the relative affinities for the three transporters may explain the different pharmacology, tolerability and efficacy observed in these early studies.

Microdialysis studies show that amitifadine markedly and persistently increases extracellular concentrations of serotonin, NE and dopamine in prefrontal cortex (Golembiowska et al., 2012). Preclinical results report that DOV 216,303 is active in tests predictive of antidepressant activity, including the mouse forced swim test and reversal of tetrabenazine-induced ptosis and locomotor depression (Skolnick et al., 2006).

In a phase II study conducted in patients with MDD, time-dependent reductions in HAMD scores were observed in both the DOV 216,303 (50 mg b.i.d.) and citalopram (20 mg b.i.d.) groups compared with baseline scores ($p < 0.0001$). However, the short (2 wk) duration of this trial makes it difficult to comment on the full clinical effect (Skolnick et al., 2006). Results from a 6-wk, multicentre, randomized, double-blind, parallel, placebo-controlled study of amitifadine have now been reported (Tran et al., 2012). In this study of 63 MDD patients, 6 wk treatment with amitifadine significantly improved MADRS total score *vs.* placebo (18.2 *vs.* 22.0; $p = 0.028$), with an overall statistical effect size of -0.601. Interestingly, a *post hoc* analysis of anhedonia items demonstrated a statistically significant difference in favour of amitifadine compared with placebo ($p = 0.049$). Amitifadine was reported to be well-tolerated, with no effect on sexual function and no serious adverse events over the 6 wk (Tran et al., 2012).

Agents for MDD must address the full symptom range

The most successful future antidepressants are those that treat all of the associated symptoms of MDD, including anxiety, sleep disturbances and cognitive dysfunction, and have minimal drug-related side-effects (Rosenzweig-Lipson et al., 2007). Minimal inhibitory effect on drug-metabolizing enzymes is also deemed an important feature of antidepressant drugs. Although the importance of co-morbid symptoms (e.g. cognitive dysfunction and anxiety) is increasingly understood and studied in other neuropsychiatric disorders, such as schizophrenia and bipolar disorders (Buchanan et al., 2005), depression research is lagging behind and is currently only in its initial stages.

Cognitive function

Recognition of cognitive dysfunction in patients with MDD has gained more importance in recent years. At the time of diagnosis of MDD, patients often suffer from altered cognitive functions of episodic memory, working memory, mental processing speed and motor response (Porter et al., 2003; Airaksinen et al., 2004, Fava et al., 2006; Mondal et al., 2007). There is growing literature on the positive and negative effects of antidepressant therapy on cognitive function in depressed patients (Fava et al., 2006; Herrera-Guzman et al., 2009, 2010). In these studies, SNRIs appear to have a greater benefit on cognition (episodic and working memory) than SSRIs (Herrera-Guzman et al., 2009), indicating that a multimodal approach may be more likely to result in an improvement in cognitive function. Moreover, a mix of preclinical and clinical research has begun to demonstrate the influential role of various serotonin receptors in the modulation of cognition, memory and mental processing. In particular, much research interest has focused on the pro-cognitive effects of 5-HT_{1A} (Ogren et al., 2008), 5-HT_6 (Fone, 2008) and, more recently, 5-HT_7 (Waters et al., 2012) antagonists. It must be noted that the roles of NE and dopamine may be at least equally important with regard to cognition and that the effects of serotonergic agents may be mediated through both a direct effect on receptors and also downstream effects on dopaminergic, cholinergic and GABAergic systems (Terry et al., 2008).

Anxiety

Anxiety and depressive disorders are also highly co-morbid and have overlapping symptom presentations. Indeed, more than half (58%) of all patients with MDD have an anxiety disorder, including generalized anxiety disorder (Kessler et al., 1996). Currently, SSRIs/SNRIs are considered first-line therapy and are effective in both anxiety and depressive states (Dunlop and Davis, 2008). However, depressed patients with high levels of anxiety generally suffer from more severe symptoms, a poorer response to treatment and greater sensitivity to side-effects than depressed patients without an anxiety disorder. These factors contribute to higher rates of treatment discontinuation and significant unmet need (Dunlop and Davis, 2008).

Neurobiochemical evidence suggests that both anxiety and depression are related to disturbances in a variety of neurochemical systems – particularly serotonergic and noradrenergic transmission and regulation (Casacalenda and Boulenger, 1998; Howland and Thase, 2005). Indeed, the involvement of these neurotransmitter systems in both normal and pathological mood states suggests a continuum from normal arousal to anxious and depressive states. Although multi-modal approaches with benzodiazepines and antidepressants has been shown to improve outcomes over monotherapy in some patients (e.g. speed of response; Dunlop and Davis 2008), it is recommended that benzodiazepines should only be used as short-term augmentation during the beginning phase of antidepressant treatment and that long-term treatment of co-morbid anxiety is better managed by antidepressants that also treat anxiety disorders (Nutt, 2010).

Despite our better understanding of the importance of recognizing and treating co-morbidities, a major barrier to research is that current clinical trials are not usually designed to compare therapies in different depression subtypes – where it is probable that multi-modal agents will have differential efficacy profiles.

Drug nomenclature

Drug nomenclature is moving toward naming an agent based on all of its therapeutically linked pharmacological properties and not by its clinical action or actions. Thus, we have moved away from the general terminology of 'antidepressants' and toward specific terms such as SSRI. Therefore, the development of multi-modal antidepressant drugs provides a dilemma with regard to nomenclature. For instance, which is the primary pharmacological property and which is secondary (or tertiary, etc.)? Also, how will these properties be reflected in the drug name? Considering that the actions of multi-modal drugs should be complementary, one way to categorize them would be by their overall effects. For example, the terms 'serotonin modulator' and 'serotonin stimulator' have been suggested for some of the new multi-modal compounds. In a recent editorial, Nutt proposed a new classification system that categorizes according to 'uni-modal' *vs.* 'multi-modal' mechanisms of action (Nutt, 2009). The prime delineator is mode of action, with subgroupings based on the number of neurotransmitter systems involved in the action of a particular drug. According to this system, antidepressants could be divided into four main categories: enzyme inhibitors (single target and multi-target); reuptake blockers (single target and multi-target); receptor-acting drugs (single target and multi-target); multi-modal drugs, which would currently be subdivided into 'reuptake and receptor antagonists' and '5-HT reuptake and 5-HT receptor blockers' (Nutt, 2009). This proposal is just one step forward in the discussions that need to occur to classify better the 'antidepressant' drugs available.

What is next?

Following the early success of the SSRIs, drug development programmes turned away from drugs with multiple actions (i.e. TCAs) and began looking for highly selective agents. Although the pathogenesis of depression remains elusive, clinical and preclinical evidence increasingly indicates that agents with a 'multi-modal' type of action are more likely to be effective against the core and co-morbid symptoms of depression. It will also be important to distinguish the efficacy of new 'multi-modal' treatments in patients with a history of TRD and patients at their first episode, or with a history of good response to antidepressants. Theoretically at least, multi-modal agents are more likely to be efficacious in patients resistant to current treatments. However, pharmaceutical companies do not generally perform trials in the treatment-resistant population.

To improve patient compliance, and therefore improve the long-term prognosis of MDD, new multi-modal drugs must address not only the problems associated with current therapy (e.g. delayed onset of action and poor tolerability), but also the other important symptoms such as anxiety and cognitive dysfunction. Finally, as we strive to tailor therapy to the individual needs of the patient, it is likely that the effects on the co-morbid symptoms will be a key factor in deciding which therapy to initiate. The potential of the new drugs to target symptoms such as anxiety and cognitive deficits, through effects on multiple receptors and transmitter systems, is an exciting advancement in MDD treatment. The challenge is to develop multi-modal drugs that have complementary therapeutic actions while avoiding those actions that cause side-effects.

Acknowledgments

This review was sponsored and funded by the Takeda Pharmaceutical Company, Ltd as part of a joint clinical development program with H. Lundbeck A/S. The author thanks Anita Chadha-Patel, PhD and The Medicine Group for assistance with manuscript preparation (literature search and editing for journal submission).

Statement of Interest

The author is co-inventor on issued US patents on triple reuptake inhibitors. The technology in these patents is not licensed at this time.

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