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Current Advances in the Treatment of Major Depression: Shift Towards Receptor Specific Drugs

Ashok Kumar Jainer, Rajkumar Kamatchi,
Marek Marzanski and Bettahalasoor Somashekar

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1.Introduction

Depression is one of the most common psychiatric disorders with a life time prevalence of 10% - 20% in the general population and women being at twice the risk of developing depression compared to men (Kessler et al., 2007). Literature suggests that prevalence of depression is higher in patients with chronic illnesses (Katon 2003). It is estimated that around 11%-15% of patients with diabetes, 15%-23% of patients with coronary artery disease, and 9%-31% of stroke patients suffer from depression. The prevalence of depression has been reported even higher among patients with chronic neurological illness such as parkinson's disease (20%-30%) and multiple sclerosis (16%- 30%).

The high prevalence of depression in the general population has an adverse impact on the community and depression affects the patients well being and their productivity in life. It is reported as the third leading cause of disability as measured by disability adjusted life years (DALYs) and is projected to become the second leading cause in 2020 (WHO 2012). Furthermore, the life time risk of suicide in patients diagnosed with depression is as high as 6% (Inskip et al., 1998). Therefore effective treatment of depression is very important to prevent disability.

The management of depressive disorder is challenging for most clinicians. Over the last 50 years, repeated attempts were made to develop a novel antidepressant, with the intention of maximising the efficacy and minimising the side-effect profile. The research has moved from time to time as in the beginning it was focussed on noradrenaline neurotransmission, later on serotonin neurotransmission. In the last decade, it has moved towards dual action and receptor specific agents. In this chapter we review and update the high quality evidence for pharmacotherapies of depressive disorder and highlight the future trends in the development of new promising antidepressants.

2. Evolution of pharmacotherapy for depression

In 1957, the antidepressant property of isoniazid was discovered serendipitously and this has led the pharmacological research to develop drugs which inhibit monoamine oxidase and drugs which block the reuptake of noradrenaline. This resulted in the development of various monoamine oxidase inhibitors (MAOI) and tricyclic antidepressants (TCA) which dominated the treatment of depression for over 30 years, predominantly TCA's. In the 1990's selective serotonin reuptake inhibitors (SSRI) were introduced and quickly they became the first line of treatment for depression. These agents were reported equally efficacious with less side-effects and are safer in overdoses. Over the last decade the research was focussed to enhance the efficacy, accelerate the onset of action and reduce the side-effects. In this regard, many newer agents were introduced with different mechanisms of action and proved very helpful in many aspects. They include noradrenaline reuptake inhibitors (NARI), serotonin and noradrenaline reuptake inhibitors (SNRI), noradrenergic and specific serotonergic antidepressant (NaSSA) and more recently agomelatine.

The combination of SSRI with another newer antidepressant has proved very effective for treatment resistant depression (Blier et al., 2010). RCTs have shown superior effectiveness for combination of antidepressant and psychological intervention (cognitive behavioural therapy) compared to psychotherapy alone (Cuijpers et al., 2009). In addition, studies have confirmed the usefulness of long term antidepressant treatment to prevent further relapses (Nierenberg et al., 2003).

The mechanism of action of currently available antidepressants is mostly monoamine based. Their efficacy is relatively modest and the benefits may be limited by poor tolerability. This has led research to search for antidepressants with different mechanisms of action including multimodal serotonergic agents, triple uptake inhibitors, neurokinin based drugs and glutamate based agents.

3. Monoamine hypothesis of depression

The monoamine hypothesis remains the main aetiological theory of depression. It suggests that depression occurs as a result of an abnormality in the monoamine neurotransmitter system in the brain. The monoamines involved are serotonin, noradrenaline and dopamine.

Numerous abnormalities in the monoamine system have been linked with depressive symptoms in patients suffering major depression. The earliest evidence came from the observation that reserpine causes depletion of monoamines and induces a state similar to depression (Healy & Savage 1998). Studies have reported abnormalities in the metabolism of these neurotransmitters as well as changes in the neuroendocrine measures which are affected by these monoamines. These include decreased plasma tryptophan levels, a precursor of serotonin, noted in untreated depressed patients (Anderson et al., 1990) and low cerebrospinal fluid (CSF) concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the metabolite of se-

rotonin, found in depressed patients who attempted suicide (Brown and Linnoila 1990). Furthermore, depletion of serotonin or noradrenaline in patients who were recovered from their depressive episode made them more vulnerable to relapses (Smith et al., 1997; Berman et al., 1999).

Monoamine theory has been supported by the receptor changes that occur during treatment with antidepressant medications whose main mechanisms of action are to either increase the synaptic levels of monoamines or to have an effect on post-synaptic receptors. Initially due to low levels of neurotransmitters, the post-synaptic receptors become supersensitive. On antidepressant treatment, the levels of neurotransmitters are increased and the receptors go into a persistent activated mode. This may be a cause of delay in the onset of action of antidepressants. During the long term treatment, the alpha-2 auto receptors in noradrenergic system become desensitized resulting in additional release of noradrenaline from the neurons. Further studies have helped to recognise the different roles of various monoamine receptors and the effects of the drugs acting on these receptors.

The possible pharmacological properties of the antidepressants acting via neurotransmitters on the various receptors are shown in Table 1.

Pharmacological properties	Possible clinical effects
Inhibition of MAO	Alleviation of depression
Inhibition of NA re-uptake	Alleviation of depression
Inhibition of 5HT re-uptake	Alleviation of depression Sexual dysfunction, anorexia, gastro-intestinal distress, headache, dizziness
Activation of 5HT _{1a} receptors	Alleviation of depression
Antagonism of 5HT ₂ receptors	Alleviation of depression, weight gain
Antagonism of 5HT ₃ receptors	Alleviation of anxiety and psychotic symptoms
Activation of 5HT ₃ receptors	Nausea/ vomiting
Antagonism at H ₁ receptors	Potential of central depressant drugs, sedation, drowsiness, confusion
Antagonism at muscarinic receptors	Blurred vision, dry mouth, sinus tachycardia, constipation, urinary retention, confusion
Antagonism at alpha 1 receptors	Postural hypotension, dizziness, reflex tachycardia, sedation, drowsiness
Antagonism at alpha 2 receptors	Alleviation of depression
(Adapted from Quasim and Kumar 1999)	

Table 1. Possible pharmacological properties of antidepressants.

4. Increasing synaptic levels of monoamines

4.1. Tricyclic Antidepressants (TCA)

Tricyclics increase the levels of monoamine neurotransmitters in the synapse by inhibiting re-uptake of both serotonin and noradrenaline back into the pre-synaptic neurons. They also act on various other receptors including cholinergic and histaminergic receptors which relate to their side-effects. They have cardiac membrane stabilising action which can cause arrhythmias and heart blocks. The use of TCAs has declined over time due to poor tolerability and high toxicity in overdoses, particularly cardiac side-effects. Repeated attempts to modify this side-effect has led to the development of Lofepramine, a relatively new TCA which has less cardiac side-effects and seems to be safer in overdose, while its efficacy remains similar to that of other tricyclics. There is good evidence that TCAs are more effective in severe depression, particularly inpatients compared to SSRI's (Geddes et al., 2002) and a small number of TCA's are still used in clinical practice.

4.2. Monoamine Oxidase Inhibitors (Irreversible MAOI)

Traditional MAOIs increase the levels of neurotransmitters by irreversibly blocking monoamine oxidase enzymes in the synapse and the enzyme blockade lasts for two weeks even after stopping MAOI. They block both MAO-A and MAO-B enzymes, not only in the nervous system but also in the gut. As a result, they have a dangerous interaction with tyramine containing foods and sympathomimetic drugs causing a hypertensive crisis. This restricts patients from consuming tyramine containing foods and certain other medications such as cold remedies and cough suppressants.

MAOIs are now used as third line drug in the treatment of depression due to these limitations. They are very useful in patients who do not respond to SSRI and TCA. It is also useful in atypical depression (depression characterised by mood changes, increased sleep and appetite, weight gain and sensitivity to rejection) and in phobic anxiety disorders. A recent review concluded that MAOI, **Phenelzine** remains as the gold standard treatment for atypical depression (Stewart 2007).

4.3. Reversible inhibitor of monoamine oxidase –Type A (RIMA)

These new generation MAOIs are more selective in their action, in that they block only MAO-A not MAO-B enzymes. The inhibition is reversible and it doesn't require the lengthy wash-out periods after stopping them. The efficacy of **Moclobemide**, the only drug currently available in this group, is similar to other MAOIs but with a much reduced possibility of hypertensive crisis. However it causes serotonin syndrome in combination with an SSRI. The therapeutic dose range is between 150-600mg/day. It is shown to produce rapid and significant improvement in both social functioning and quality of life (Lorinquivst et al., 1994).

5. Selective Serotonin Reuptake Inhibitors (SSRI)

The discovery of SSRIs in 1989 was a turning point in the treatment of depression. It switched the emphasis from noradrenergic to serotonergic system and stimulated research on serotonin receptors. SSRIs are more selective in inhibiting only serotonin reuptake and have no action on histamine, adrenaline and cholinergic receptors. Therefore their tolerability is much better compared to TCAs or MAOIs. They have similar efficacy to older drugs, but better tolerability and safety in overdoses and have become the first line of treatment for depression over the last two decades. There are six drugs available in this group namely **fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram and escitalopram**.

Although these six medications differ in their chemical structure and pharmacokinetics (Van Harten 1993), there are no major differences in their efficacy or side-effect profile (Aguglia et al., 1993). The common side-effects include gastro-intestinal problems, dry mouth, sweating, headache, asthenia and sexual dysfunction such as ejaculatory delay/failure and anorgasmia. SSRIs have fewer drug interactions compared to older drugs and the most important one is with MAOI when concurrent administration may cause serotonin syndrome. Therefore MAOIs and RIMA are contraindicated in combination with SSRIs and there should be a washout period before swapping them.

The safety profile of these drugs was found to be similar (Price et al., 1996) and they do not cause physical dependence. However, abrupt withdrawal or marked reduction in the dose of SSRI may lead to the development of discontinuation symptoms. The common symptoms are dizziness, paraesthesia, tremors, anxiety, nausea and increased heart rate which may last for up to 10 days. Paroxetine causes discontinuation symptoms more often (5.1%) than other SSRIs (0.06- 0.9%).

Escitalopram, the active isomer of citalopram, is a highly selective SSRI and has shown better efficacy in the treatment of severe depression, both in effect size and time of onset of action (Azorin et al., 2004). In a recent multiple-treatment meta-analysis, escitalopram and sertraline have shown the best profile of acceptability and sertraline had the most favourable balance between benefits, tolerability and cost-effectiveness (Cipriani et al., 2009).

6. Serotonin Antagonist and Reuptake Inhibitors (SARI)

Trazodone and nefazodone belong to this group and chemically they are phenylpiperazines. They have dual action on the serotonergic system, as they are potent 5HT₂ receptor antagonists and weak reuptake inhibitors. This combination of actions enhances 5HT_{1a} mediated neurotransmission and is thus effective in the treatment of depression.

Trazodone has been available since 1998 but it is used infrequently as antidepressant because of its sedating property. Rather it is been prescribed in lower doses as hypnotic in addition to SSRIs. Sexual side-effects are less frequent but it can cause priapism in some

patients. A recent review (Papakostas & Fava 2007) showed that trazodone has efficacy comparable to SSRIs and nefazodone. It is also relatively safe in overdose.

Nefazodone is a derivative of trazodone and is chemically related. It is found to be as effective as TCAs and superior to placebo in daily doses of 200-600mgs (Rickels et al., 1995). Sexual dysfunction was less reported with nefazodone compared with other antidepressants and there were no reports of priapism (Baldwin et al., 1997). It is less sedating than trazodone. However concerns regarding its hepatotoxicity led to withdrawal of nefazodone from the market in most countries.

7. Noradrenaline Reuptake Inhibitors (NARI)

Reboxetine is similar in structure to fluoxetine but it is a relatively selective noradrenaline reuptake inhibitor. Its therapeutic effect is mainly through increasing noradrenaline neurotransmission and it has no interaction with other receptors such as histaminergic, muscarinic or alpha 1, which were responsible for most side-effects associated with TCAs. Therefore reboxetine is useful for patients who could not tolerate tricyclics or who have been treatment resistant to SSRIs.

Reboxetine is equally effective as TCAs in both hospital patients and outpatients (Berzowski et al., 1997; Dubini et al., 1997) and has better efficacy than fluoxetine. It also helps in alleviating anxiety symptoms associated with depression. It has moderately alerting effect and improves the motivation of the patients. The main side-effects are linked to sympathetic overstimulation and include dry mouth, insomnia, sweating, tachycardia, vertigo, urinary hesitancy and impotence. The daily dose range is 4-12mgs.

8. Selective Serotonin and Noradrenaline Reuptake Inhibitors (SNRI)

SNRIs have dual action and inhibit both serotonin and noradrenaline reuptake. They do not act on muscarinic, histaminic or adrenergic receptors. As a result they have more benefits and less side-effects compared to other antidepressants. Venlafaxine, duloxetine and milnacipran belong to this group.

Venlafaxine, a phenylethylamine, inhibits the reuptake of 5HT and NA and at higher doses inhibits the reuptake of dopamine. It has a rapid onset of action and improvement may be noticed within the first week of treatment. This is because of the fast down-regulation of beta receptors induced by venlafaxine, which usually occurs only during long term treatment with other antidepressants (Holliday 1995). Venlafaxine is as effective as imipramine or fluoxetine in doses ranging from 75mgs to 375mgs/day (Guelfi et al., 1995). It is better tolerated compared to TCAs and safer in overdoses. It has less sedative and proconvulsant effects and shows minimal drug interactions. Venlafaxine is also effective in the therapy of treatment resistant depression (Nierenberg et al., 1994).

Desvenlafaxine, a synthetic metabolite of venlafaxine, is a new SNRI available since 2008. Studies have reported that it has short-term efficacy in major depression (Thase et al., 2009) and could improve the social functioning of the patients (Soares et al., 2009).

Duloxetine, another SNRI, is considered as the most potent in this group. It blocks both neurotransmitters equally, whereas venlafaxine has a stronger tendency towards serotonergic system and milnacipran towards noradrenergic system (Nierenberg et al., 1994). A latest review reported that duloxetine is safe and effective in the acute phase treatment of depression at doses of 40-60mg/day (Mallinckrodt et al., 2006). However it appears to be less effective compared to venlafaxine in both remission and response rates (Vis et al., 2005).

Milnacipran, another drug in this group, is reported to be as effective as TCAs with a 65% response rate and has slightly superior efficacy to SSRIs (Montgomery et al., 1994; Lopes-Ibor et al., 1996). A recent meta-analysis suggested that milnacipran has equal efficacy and tolerability compared to other antidepressants but can be slightly more favourable to TCAs in terms of adverse effects (Nakagawa et al., 2008). Dysuria and headache are the common side-effects.

9. Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)

Mirtazapine and mianserin belong to this group. Mianserin is not used in most countries because of its hepatotoxicity and the risk of neutropenia. Thus mirtazapine is the only agent available in this group.

Mirtazapine has unique pharmacological properties. It increases the release of serotonin and noradrenaline by blocking central alpha 2 auto and heteroreceptors. It has a marginal affinity for alpha 1 receptor and a low affinity for 5HT1a receptor but good affinity for 5HT2 and 5HT3 receptors. The antidepressant effect appears to be a result of increased serotonin and noradrenaline neurotransmission (De Boer & Ruigt 1995). Due to its antihistaminergic action, it acts as a relatively sedative antidepressant although this effect is diminished at higher doses. It also blocks 5HT2 and 5HT3 receptors; therefore the sexual side-effects and nausea are less common compared to SSRIs (Chen et al., 2008).

Mirtazapine has a more rapid onset of action (Thase et al., 2010) and is equally effective as SSRIs (Papakostas et al., 2008). It also showed higher remission rates compared to SSRIs. Its side-effects are relatively mild and transient.

10. Dopamine and Noradrenaline Reuptake Inhibitors (DNRI)

Bupropion is another dual acting agent which inhibits reuptake of dopamine and noradrenaline. It is been used as antidepressant in some countries and in smoking cessation clinics. Its metabolite hydroxybupropion is a potent reuptake inhibitor and it has low receptor blocking effects. It is useful in the treatment of bipolar depression, depression with psycho-

motor retardation and atypical depression because of its dopamine related activating properties. The main side-effects are caused by dopamine over-stimulation and include nausea, insomnia, agitation, dry mouth, weight loss and psychosis. It also lowers the seizure threshold and fits can occur in 0.5% of patients. In overdoses it leads to hallucinations, tachycardia, seizures and rarely death (Harris et al., 1997; Shrier et al., 2000).

Bupropion was found to be as equally effective and tolerable as SSRIs (Thase et al., 2005). It may be beneficial for patients with symptoms of sleepiness, fatigue, low energy, anhedonia and loss of interest (Papakostas et al., 2006; Nutt et al., 2007).

11. Serotonin reuptake inhibitor and 5HT1a receptor partial agonists

Vilazodone is a relatively new antidepressant which has been available for a year in the United States. It has dual action of inhibiting serotonin reuptake and partial agonism at 5HT1a receptors. It does not cause weight gain and claimed not to cause any sexual side-effects. Nevertheless, compared to other antidepressants, the data regarding its efficacy are limited and more research is required.

12. Melatonin based therapy –Agomelatine

In the last decade, advances in the understanding of the pathophysiology of depression including genetic, neurobiological and neuroimaging studies shifted the focus of research from the monoamines to different theories of depression. One of them assumes that disturbances in the circadian rhythms may play a significant role in the pathogenesis of depression.

The links between circadian disturbances and symptoms of depression such as delay in sleep onset, early morning waking, fatigue during the day, blunting of normal peaks in subjective energy, mood and alertness are very strong (Germain and Kupfer 2008). Circadian disturbances affect the secretory rhythms of various neuroendocrine hormones such as melatonin, cortisol and noradrenaline. There are also changes in the diurnal variations of core body temperature and plasma cortisol levels. If this internal system desynchronises, the timing of various circadian rhythms is out of phase resulting in depressed mood, sleep changes and impaired neurocognition (Czeisler et al., 2005). Therefore any treatments of depression focusing on circadian rhythm not only restore the sleep-wake cycle but also will have substantial improvements in mood, cognition and day-time fatigue (Hickie & Davenport, 1999).

Melatonin is a hormone naturally secreted by the pineal gland in the body. Its secretion is usually high at night time in normal individuals. It has an important role in the regulation of circadian timing systems by binding to melatonin receptors (MT1 and MT2) in the brain (Weaver 1999). Based on this idea, melatonin based therapies have been developed recently for the treatment of depression.

Agomelatine is a new antidepressant with a unique mechanism of action. It is a selective agonist at MT1 and MT2 receptors and an antagonist at 5HT2b and 5HT2c receptors. It has a rapid absorption rate and peak plasma levels are achieved between 45 and 90min after a single oral dose of 25-50mgs. It has clinically significant antidepressant and anxiolytic effects (de Bodinat et al., 2010; De Beradis et al., 2011). The clinical benefits occur from the combined effects of melatonin and monoamine actions as well as non-circadian processes such as increased production of brain- derived neurotrophic factors (Palzanis et al., 2010). Agomelatine has similar efficacy to SSRIs (Kasper et al., 2010; Hale et al., 2010) and venlafaxine (Kennedy et al., 2008). The common side-effects include nausea, dizziness and headache.

13. Combination treatments for treatment resistant depression

Although the newer antidepressants have better efficacy in the treatment of depression, nearly one third of patients fail to achieve remission. Moreover complete remission is not always possible and partially treated patients are at higher risk of relapse, experience more personal and socioeconomic problems and have poor quality of life. A patient is considered to suffer treatment resistant depression (TRD) if they fail to achieve remission with adequate trials of two different classes of antidepressants. There are few strategies available to tackle treatment resistance including both pharmacological and non-pharmacological therapies.

Combination of two different antidepressants to treat resistant depression has become a common practice. A recent systematic review (Rocha et al., 2012) showed that antidepressant combination was more effective than a single antidepressant in achieving remission. The superior combination was mirtazapine with SSRI. The other effective combinations are mirtazapine and SNRI, SSRI with bupropion, TCA with SSRI and bupropion with venlafaxine or mirtazapine.

Combination of an antidepressant with an antipsychotic is another useful strategy in treating resistant depression. 5HT2a/ 5HT2c antagonist effect of atypical antipsychotics potentiate the efficacy of antidepressants and at times counteract the side-effects of SSRIs. The most useful combination appears to be an SSRI with an atypical antipsychotic (Thase 2002). Weight gain and sedation are the common adverse effects.

The **augmentation** of an antidepressant with lithium, triiodothyronine and omega-3 fatty acids have also been beneficial in some patients. Combinations of pharmacological and non-pharmacological treatments are described in section 14 below.

14. Advances in non-pharmacological treatments of depression

Psychological therapies and physical (non- pharmacological) treatments have been developed and refined in the last few decades. In this section, the evidence of their efficacy in the treatment of depression will be reviewed.

14.1. Psychological interventions

Many psychological interventions have been used in the treatment of depression. These include supportive counselling, cognitive – behavioural therapy (CBT), interpersonal psychotherapy (IPT), mindfulness- based cognitive therapy, problem solving therapy and long term psychodynamic psychotherapy. However, only CBT and IPT have good quality evidence in the treatment of depression either as monotherapy or in combination with antidepressants (Sagar et al., 2009).

Cognitive- behavioural therapy has become a standard treatment for mild and moderate depressive disorders. It may be particularly useful for patients who experience relapse in spite of continuous anti-depressant treatment or for patients with partial response. CBT combines elements from both cognitive theory and behaviour theory of depression. According to cognitive theory maladaptive thinking with regard to self, future and environment (cognitive triad) causes depression. These “core beliefs” become active when people face certain life situations and lead to depressed mood mediated by negative automatic thoughts associated with them. CBT helps patients to understand the links between the thoughts, the emotions and the consequent behaviours and then equip them with alternative thinking styles to cope with day to day problems.

CBT has good efficacy in both achieving remission and reducing the risk of recurrence of depression (Vittengl et al., 2009; Hollon et al., 2005). Combination of CBT and antidepressant is more effective than CBT alone (Cuijpers et al., 2009). Therefore current treatment guidelines recommend combining CBT with antidepressant in partial remissions or treatment resistant patients. CBT can also be implemented in different ways such as internet based CBT, self-help guidebooks or even telephone CBT which can be helpful in primary care (Kessler et al., 2009; Simon et al., 2009).

Interpersonal psychotherapy is another effective psychological intervention used in the treatment of depression. IPT incorporates elements from psychodynamic psychotherapy and CBT. Similar to CBT, it is time-limited and includes structured sessions and homework tasks (Weissman et al., 2007). The therapy focuses on current interpersonal relations and their influence in the development of depression. It frequently focuses on role changes (e.g. job loss, becoming a new mother) and role disputes (e.g. relationship problems, work difficulties). It is equally as effective as CBT in mild and moderate depression. However, CBT has a better response rate in severely depressed patients (Luty et al., 2007). The response rate for combination of interpersonal psychotherapy and medication is higher than IPT or medication alone (Schramm et al., 2007) and the benefits are sustained even after remission (Frank et al., 2007).

14.2. Physical treatments

Physical treatments for depression have been increasingly acknowledged in recent years. They include electro- convulsive therapy (ECT), transcranial magnetic stimulation (TMS), deep brain stimulation, magneto-convulsive therapy and vagus nerve stimulation.

Electro-convulsive therapy has been a well recognised treatment for depression even before the discovery of psychotropic drugs. However over the years its usage has declined and now it is indicated mainly for severe depression with a high risk of suicide, depressive stupor, treatment resistant depression and patients in danger to their physical health secondary to poor dietary intake. At the same time, ECT has become a more sophisticated procedure with advances in the field of anaesthesia and improved technology of ECT machines. ECT is a rapid and effective treatment for major depression. A recent meta-analysis showed ECT has significant superiority to antidepressants in both severe and treatment resistant depression (Pagnin et al., 2008). The most common side-effects reported are headaches and short term confusion following the treatment. In some patients, there is an increased risk of long-term memory loss but the evidence base for this side-effect remains controversial.

Transcranial magnetic stimulation (TMS) has now been approved in United States for the treatment of major depression, particularly for patients who have not responded to antidepressant medications (Kim et al., 2009). TMS produces a magnetic field around brain and the main target areas are dorsolateral prefrontal cortex in both sides of the brain. Two meta-analyses (Kim et al., 2009; Slotema et al., 2010) showed that repetitive-TMS has higher efficacy than placebo and comparable efficacy to antidepressants. However it was less effective than ECT. Patients reported headaches following the treatments and seizures can be a rare side-effect.

Deep brain stimulation, magneto-convulsive therapy and vagus nerve stimulation appear to be promising in the treatment of depression but they are all still in the experimental stages.

In deep brain stimulation, electrodes are implanted in the brain and controlled by the internal pulse generator. The stimulation modulates the neurotransmission in the cortico –striatal – thalamic- cortical circuit. It is a reversible procedure and the stimulation can be adjusted according to the patient's needs (Giacobbe et al., 2006).

Magneto-convulsive therapy is another experimental treatment where seizures are induced by repetitive-TMS in a controlled way targeting the brain structures essential for treatment response, particularly the temporal lobes.

In vagus nerve stimulation, bipolar electrodes are attached to the left cervical vagus nerve and stimulation periods are controlled. The side-effects include hoarseness of voice, pain, cough and dysphagia.

15. The future of pharmacotherapy of depression

Despite the advances in the treatment of depression, the efficacy of currently available antidepressants is still relatively modest and there are patients who do not respond to them. The limitations of the monoamine based antidepressants include slow onset of action, poor impact on certain symptoms such as disturbed sleep and fatigue and they cause multiple side-effects. Numerous innovative approaches have been studied looking at new and different

mechanisms for the treatment of depression. Some of these promising approaches are discussed below.

15.1. Selective versus multi-transmitter antidepressants

It has always been a debate whether selective neurotransmission is better than multiple neurotransmission. This issue of selectivity versus efficacy has re-emerged as the newer antidepressants are less selective than SSRIs but relatively more selective than the TCAs.

Burke (2004) reviewed the topic comparing SSRIs against TCAs and somewhat more selective venlafaxine. The review concluded that SSRIs' success is presumably not because of their efficacy, but rather to ease of use, minimal need for titration, better tolerability and improved safety in overdose. The difference in tolerability is due to the fact that TCAs act on multiple receptors causing more adverse effects. In comparing SSRIs with venlafaxine, Thase et al., 2001 found that venlafaxine had higher remission rates and they attributed this to its "dual action". However venlafaxine does not have substantial effects on noradrenaline until the dose is increased above 150mg/day and therefore technically it cannot be considered as a dual acting agent at lower doses.

Perhaps a better way to increase the efficacy is to target the specific receptor rather than increasing overall neurotransmission. If a drug acts only at the specific receptor and alleviates the depressive symptoms then its unnecessary action at other receptors can be avoided. Therefore more receptor specific drugs have to be designed rather than those aiming at greater than previous neurotransmission.

One approach is developing new formulations with existing antidepressants. Some of these are more acceptable to patients (fluoxetine once weekly, paroxetine CR), some have faster onset of actions (mirtazapine soluble tablets & intravenous preparations) and others such as venlafaxine XL have clear pharmacokinetic benefits (Norman & Oliver 2004).

15.2. Other agents in development

The other approach to address the issue of efficacy is developing new agents. The agents in development include multimodal serotonergic agents, triple uptake inhibitors, neurokinin (NK1) antagonists, glutamate antagonists, dopamine agonists and antiglucocorticoid agents.

Multimodal serotonergic agents are simply an extension of SSRIs and SNRIs. They have both serotonin reuptake inhibition and either blocks 5HT_{2a} receptor and/or act as partial agonist at 5HT_{1a} receptor. **Vilazodone**, the first agent of this group, is already available in clinical practice and there are few other drugs in development.

Triple uptake inhibitors combine the inhibition of serotonin, noradrenaline and dopamine transporters. Their development is based on the assumption that targeting dopamine neurotransmission would enhance overall efficacy and diminish certain symptoms such as anhedonia, apathy, sleepiness and fatigue as well as counteract sexual side-effects induced by SSRI (Fava et al., 2007). **Sibutramine** is the only available drug with triple uptake inhibition

and it is currently used in weight loss therapy. One of the limitations associated with this mechanism might be the risk of abuse linked with increased dopamine neurotransmission.

Neurokinin receptors (NK1 and NK2) and their endogenous ligand **Substance P** are found in brain areas known to be involved in the regulation of mood, stress and anxiety responses (Bergstrom et al., 2004). However NK1 antagonist **aprepitant** failed to show greater efficacy to placebo (Keller et al., 2006). Currently studies focusing on NK2 antagonists are underway.

Glutamate modulating agents such as **ketamine** (NMDA antagonist) generated significant interest in the field when rapid and sustained antidepressant effects were seen after injections of ketamine (Berman et al., 1999). Another NMDA antagonist and dopaminergic drug **amantadine** showed efficacy in depressed imipramine non-responders (Rogoz et al., 2007). It may be useful in depressed patients with prominent cognitive dysfunction. The main limiting factor in using these agents is the risk of inducing psychotic symptoms due to their hallucinogenic properties (Smith 2008).

Dopamine agonists, similar to DNRI bupropion, seem to be promising in the treatment of depression. A review showed that dopamine agonists had anxiolytic, antidepressive and anhedonic effects which were related to its action on dopamine D2 and D3 receptors (Lenke 2007). Two agents, **ropinirole** and **pramipexole** proved efficacy as additional treatment to mood stabiliser in bipolar depression but further research is required to prove their efficacy and usefulness as antidepressants.

Biological studies of depression have shown that the secretion of hypothalamic neuropeptides such as corticotrophin releasing hormone (CRH) and vasopressin is elevated in depressed patients. CRH acting through CRH1 receptor may cause symptoms of depression. Depressed patients also have increased cortisol levels which might be responsible for psychotic symptoms of depression. A review of the hypothesis that **CRH1 receptor antagonists and antiglucocorticoid agents** may be useful in the treatment of depression supports this direction in the development of future antidepressants (Nemeroff 2002).

16. Conclusions

Major depressive disorder is a complex psychiatric condition, with multiple aetiological factors. The pathophysiology of depression is still evolving with ongoing molecular, genetic and neuroimaging studies. Evidence from neurobiological studies indicates that monoamine hypothesis of depression cannot fully explain the causation of depression. Further research into the aetiology of depression beyond monoamine hypothesis may provide new directions in developing novel agents in the treatment of major depressive disorder.

The initial focus on increasing the synaptic levels of neurotransmitters, especially serotonin and noradrenaline, has already shifted towards dual action and receptor specific antidepressants. Although there have been considerable advances in the treatment of depression since TCAs were discovered in the 1950's, the current treatments are not fully satisfactory for either patients or clinicians. Research evidence on several new pharmacological and non-

pharmacological interventions is still preliminary and further studies are needed to prove their actual benefits.

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Author details

Ashok Kumar Jainer¹, Rajkumar Kamatchi^{1,2}, Marek Marzanski^{1,2} and Bettahalasoor Somashekar¹

1 Coventry & Warwickshire Partnership NHS Trust, Coventry, UK

2 Warwick Medical School, Coventry, UK

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