Antidepressant Compounds: A Critical Review

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Abstract

Major depression is a commonly encountered mental disorder in clinical practice. Although choices of antidepressant drugs appear to be many, all current antidepressant drugs have essentially similar mechanisms of action through the monoaminergic pathways. There remain a significant number of patients not benefiting from the current antidepressant compounds. Considering that major depression is likely to be a multisystem disorder, the current lack of antidepressant drugs with alternate mechanisms of action hinders treatment of drug resistance cases, residual symptoms and incomplete remission. New drugs are also needed to address many of the areas of impairment not responsive to current antidepressant drugs, such as memory impairment, impaired executive function and compromised endurance to daily life stress. To develop such new antidepressant drugs, ‘out of the box’ thinking is critical.

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Major depressive disorder (MDD) is a common mental disorder in clinical practice. However, it is difficult to know how many patients suffering from major depression are not diagnosed or misdiagnosed and therefore not treated. Many studies suggest that major depression is much more common than reported. For example, the high prevalence of depression in college students [1–3] has been commonly noticed by school clinic physicians, but there are few systematic studies of this phenomenon or reports in medical journals. Similarly, depression associated with other medical problems, such as stroke, cardiac and gastroenterological problems, as well as somatic presentation of depression pushed into the medically unexplained syndromes, is now known to be quite common [4, 5]. Depression is already the 2nd leading cause of disability as measured by years lived with disability. It was estimated that by the year 2020, depression would reach 2nd place in the ranking of disability-adjusted life years (i.e. the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability) calculated for all ages. At the first Global Mental Health Summit in Athens, Greece, September 2009, the World Health Organization predicted that within 20 years more people would be affected by depression than by any other health problem.
For the ones fortunate enough to be diagnosed and treated, there also exist problems of inadequate treatment in terms of dosages and duration of treatment, drug noncompliance, relapses, drug side effects, incomplete resolution, residual symptoms, drug resistance and compromised ability to resist stress in life. Deficiencies in the current selection of antidepressant drugs are many. For example, MDD patients who did not respond to the first 2 antidepressant treatments had a less than 15% chance of responding to subsequent treatments [6]. Lowering of relapse rate, bipolar switching issues and resolution of residual symptoms (including executive function and memory impairments) would probably require new drug targets. Some of these issues appear to be connected. For example, a greater number of residual symptoms is associated with a greater relapse rate [7]. Bipolar switching into mania has been reported to affect as much as one third of the bipolar inpatient population [8]. While it is widely acknowledged that current antidepressants do not protect against the emergence of manic symptoms [9], the risk of switching to mania was higher during tricyclic antidepressant (TCA) treatment (36%) compared to nontricyclic treatment (17%) [8]. Memory impairment is a relatively robust finding in depressed patients. Additionally, there is preferential processing of negative affective material and exaggerated response to negative feedback in depressed subjects [10]. Many of these symptoms can be dissociated from mood and do not always resolve with current antidepressant treatment. Considering all these problems, it is clear that response to current antidepressant drugs is far from satisfactory.

Of all the problems surrounding the management of major depression, what is urgently needed is the development of new antidepressant drugs to address many of the inadequacies of the existing ones. New antidepressant compounds with efficacy in resistant cases, easing residual symptoms, and with faster onset of action are most needed. Antidepressant drugs targeting those symptoms not responsive to current medications, such as memory, energy and executive function impairment, would be very useful. New antidepressants effective in long-term maintenance with minimum side effects or adverse reactions would also help. Pharmacologically, these new antidepressant drugs should possess a core mechanism of action different from the existing ones, therefore allowing clinicians to have a real alternate choice in cases resistant to or with incomplete response to existing antidepressant drugs. This chapter reviews and discusses such a possibility.

**Traditional Paths for Development of Antidepressant Compounds**

**Exploitation of the Serotonin Transporter in Antidepressant Drug Development**

The TCAs, the selective serotonin reuptake inhibitors (SSRIs) and the serotonin-nor-epinephrine reuptake inhibitors (SNRIs) all block the reuptake of serotonin (5-HT) potently. The 3-dimensional molecular structure of these drugs enables them to bind
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to the 5-HT transporter with high affinity. Binding to the 5-HT transporter causes conformational change of the transporter protein resulting in an interference of the passage of the 5-HT molecule through the transporter. The TCAs and the earlier SSRIs appear to bind to a common site of the 5-HT transporter protein. Some of the critical amino acids of the transporter protein contributing to this binding site have been identified [11–13]. Interestingly, there also appears to be a second site. The active enantiomer of citalopram, escitalopram, has been shown to bind to this second site and appears to cause additional changes in the kinetics of association and dissociation of the antidepressant compound itself from the first binding site. This change in the binding kinetics has been suggested to convey additional antidepressant advantage (for a review, see Tang and Helmeste [14]) making escitalopram superior to its racemic parent citalopram and other antidepressant drugs of the 5-HT and norepinephrine (NE) reuptake inhibitory class [15–18].

Evolution of the 5-HT reuptake inhibitory type of antidepressant drugs reflects attempts to develop new antidepressant compounds with higher potency and specificity and to minimize side effects, including cytochrome P450 enzyme inhibition. With good choices among the various SSRIs and SNRIs, the need for additional new SSRI compounds appears to be quite limited. There have been some attempts to develop new antidepressant compounds with triple [5-HT, NE and dopamine (DA)] reuptake inhibition [19]. It is foreseeable that such effort will not provide any additional benefits in terms of efficacy, as it will not bring in a new mechanism of action. The SSRI sertraline already possesses respectable DA uptake inhibition but has not been shown to greatly exceed other SSRIs in terms of efficacy [20].

Serotonin Receptors as Potential Antidepressant Drug Targets

There are 7 known classes of 5-HT receptors. Some 5-HT receptors have been suspected to play an important role in the maintenance of mood. Also, many antidepressant drugs and anti-anxiety drugs possess moderate to high affinities for various 5-HT receptors, including 5-HT1A, 5-HT2A, 5-HT2B and 5-HT4 receptors and some are not monoamine reuptake blockers. Examples of new compounds with antidepressant properties but which are not monoamine reuptake blockers include agomelatine and aripiprazole, which have affinity for 5-HT1A and 5-HT2C receptors. How these compounds produce antidepressant action through 5-HT receptors or whether the 5-HT receptor actions are essential for their antidepressant actions is far from clear [21–23]. Agomelatine, for example, is also an agonist at melatonin MT1 and MT2 receptors and improves sleep disturbance in depression [24].

In considering 5-HT receptors as antidepressant targets, it is important to distinguish between the acute and chronic effects as they could be quite different. The acute and chronic effects of antidepressant drugs on 5-HT receptors were examined in the early 1980s when radioactive antagonists with high specific activity became
available. Tang and coworkers [25–28] screened all the available antidepressant compounds for their binding affinities to 5-HT and NE receptors and compared their acute and chronic effects on these receptors. It was discovered that the acute and chronic effects of antidepressant compounds on 5-HT receptors were quite different indeed. Furthermore, the effects of some of these antidepressant compounds in reducing the density of 5-HT$_2$ receptors were not dependent on the presynaptic 5-HT input, as raphe lesions failed to interfere with this effect [29]. The differential acute and chronic effects of antidepressant compounds on 5-HT receptors were suspected to be related to the latency of antidepressant therapeutic action which may take up to 2 weeks or more.

The more detailed actions of antidepressant compounds on various 5-HT receptor subtypes were examined in many later experiments. It seems that at least 3 5-HT receptor subtypes are implicated in the antidepressant action of these compounds, namely 5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_{2C}$. Interestingly and paradoxically, both agonists and antagonists for these 5-HT receptor subtypes have been reported to have potential antidepressant effects when tested in animal models. For example, both stimulation and blockade of the 5-HT$_{1A}$ receptor may result in an antidepressant action, and both agonist and antagonistic action at 5-HT$_{2C}$ and 5-HT$_{2A}$ may also lead to an antidepressant effect. Buspirone is a 5-HT$_{1A}$ receptor agonist, trazadone is a 5-HT$_{2A/2C}$ receptor antagonist, agomelatine is a 5-HT$_{2C}$ receptor antagonist, and aripiprazole is a partial agonist with high intrinsic activity at 5-HT$_{1A}$, while being a 5-HT$_{2A}$ receptor antagonist [30–33]. This seemingly paradoxical action on 5-HT receptor subtypes reminds us of the earlier paradoxical observation that a 5-HT uptake enhancer, not a blocker, was also an antidepressant. It is quite possible that the presence of other non-5-HT inputs might play an important role in determining the final pharmacological action of these 5-HT agonists and antagonists on the same 5-HT receptor. In fact, there are experiments supporting this hypothesis.

As a recent example, agomelatine, an antidepressant that has recently been approved by the European Medicines Commission, is a potent melatonin receptor agonist with Ki values of 0.12 and 0.10 nm for the melatonin MT$_1$ and MT$_2$ receptors, respectively. It is also a potent 5-HT$_{2C}$ receptor antagonist (pKi = 6.2) in a dose that corresponds to its antidepressant and anxiolytic effects in rodents [32, 34]. This combination of melatonin receptor activation with 5-HT$_{2C}$ receptor antagonism underlies its pharmacological profile in which the early resynchronization of the sleep profile might be explained by the augmentation of the melatonergic response, while the mood effect is related to the reduction in the 5-HT$_{2C}$ receptor activity in the prefrontal cortex. Experimental studies have shown that the chronic administration of agomelatine is linked to the increase in the release of NE and DA from the prefrontal cortex without any changes in 5-HT function. This could be explained by the indirect effects on NE and DA release from this brain region by the blockade of 5-HT$_{2C}$ receptors which results in an increased outflow of these catecholamines from the frontal cortex. Recent studies have also shown that agomelatine counteracts the adverse effects of
stress on hippocampal neurogenesis in rodents [35]. Further large-scale clinical trials of agomelatine on MDD cases resistant to other antidepressant drugs will be needed to confirm its status as a new antidepressant drug with an alternate mechanism of action [36].

Other potential compounds in this category include p11 (an inducible adaptor protein), which increases localization of the serotonin 5-HT$_{1B}$ receptor at the cell surface and increases 5-HT$_{1B}$ receptor function. p11 knockout mice exhibit a depression-like phenotype and are resistant to antidepressant treatment [37].

The TREK-1 potassium channel which influences the excitability of individual neurons is another example of a new target for antidepressant drug development. TREK-1 is inhibited by therapeutic doses of SSRIs and mice lacking TREK-1 exhibit a depression-resistant profile, such as blunted cortisol response to stress. However, a reasonable worry is that if these brain proteins have too wide a distribution in the brain (and regulate other non-mood-related functions), then unwanted side effects may occur which would prevent long-term therapeutic usage. TREK-1, for example, has been implicated in neuroprotection and general anesthesia. Whether drugs targeting TREK-1 would cause undesirable side effects by disrupting other brain functions is one of many considerations in the development of such new antidepressant agents [38–40].

The Role of GABA in Antidepressant Action

Neuroanatomical, neurochemical, neurophysiological and behavioral data have confirmed the inhibitory action of GABAergic neurons on endogenous DA release. Dopaminergic mesolimbic and mesocortical systems are fundamental in hedonia and motivation. The inability of 5-HT to stimulate nucleus accumbens DA release has been proposed to be a factor in depression. The decrease in DA release has been suggested to be responsible for the symptoms of anhedonia and decrease in motivation. As 5-HT exerts an inhibitory action on GABA interneurons through 5-HT$_{2C}$ receptors, antagonism of 5-HT$_{2C}$ or subsensitivity of these receptors would release the NE and DA pathways from inhibition by the GABA interneurons [41]. While the release of DA and NE pathways from inhibition was proposed to be an important factor in the mood and motivation effect of antidepressant drugs, it may explain why antidepressant drugs might activate psychosis (through the DA effect) in some bipolar or schizophrenic patients [42]. However, bupropion, an antidepressant drug which possesses ‘dopaminergic’ action, seemed to have no effect on schizophrenic symptoms [43]. This suggests that activation of psychosis may not be a serious concern for all drugs in this category when their 5-HT action results in the enhancement of DA transmission. However, whether it is an agonistic or rather an antagonistic action that is required on the 5-HT$_{2C}$ receptor to create an antidepressant action is still far from conclusive at this point. Both agents possessing agonist or antagonist properties on the 5-HT$_{2C}$ receptor have been suggested to carry antidepressant potential [44–46]. Trazodone and nefazodone are weak 5-HT$_{2C}$ receptor antagonists and have
been shown to be useful in the treatment of milder cases of depression [47, 48]. It is important to mention that agents with single 5-HT$_{1A}$, 5-HT$_{2A}$, or 5-HT$_{2C}$ receptor action have yet to be tested clinically for true antidepressant action.

With regard to specific GABA receptor subtypes, GABA$_B$ receptor antagonists have been suggested to be antidepressants [49, 50]. SGS742, the first GABA$_B$ receptor antagonist in a clinical trial, has shown positive effect for improvement of attention and working memory in patients with mild cognitive impairment [49]. By contrast, the GABA$_B$ receptor agonist baclofen blocked the antidepressant effects of GABA$_B$ receptor antagonists in animal studies [50], and GABA$_B$ but not GABA$_A$ receptors appear to be involved in rodent models of antidepressant action [51]. Benzodiazepines have little or no antidepressant effects by themselves, but antidepressant-benzodiazepine combination therapy was found to lead to fewer dropouts and less depression severity in major depression [52].

*Increase or Decrease in 5-HT Neurotransmission after Antidepressant Treatment*

Another area of interest in considering the 5-HT pathway as an antidepressant drug target is whether 5-HT neurotransmission is enhanced, downregulated or modulated after antidepressant treatment. According to the traditional amine theory of depression, central amine deficiency causes symptoms of major depression. 5-HT reuptake inhibition by antidepressant drugs results in a synaptic 5-HT elevation and therefore 5-HT neurotransmission enhancement. Potentiation of 5-HT neurotransmission after chronic antidepressant treatment indeed has been demonstrated in physiological paradigms. However, this simplistic interpretation ignored the potential receptor changes after chronic drug treatment. Receptor binding studies in animals treated with chronic antidepressant drugs suggested that the density of 5-HT$_2$ receptors is actually decreased after chronic antidepressant treatment [26]. A decrease in 5-HT$_2$ receptor density would suggest a decrease in 5-HT transmission through the 5-HT$_2$ receptors. The most intriguing finding in arguing against a required increase in 5-HT neurotransmission for antidepressant action is tianeptine. A 5-HT reuptake enhancer, tianeptine enhances the reuptake of 5-HT (acutely) instead of inhibiting it, thus opposite to the action of SSRIs. To reconcile these conflicting findings, changes in other important central nervous system pathways such as DA secondary to changes in 5-HT neurotransmission would need to be examined. Indeed, tianeptine has been reported to enhance the extracellular concentration of DA in the nucleus accumbens [53, 54]. The DA and glutamatergic effects of tianeptine after chronic treatment are considered to be important for its antidepressant action [55]. Furthermore, while 5-HT seems to be central to many current antidepressant drug actions, it is important to mention that presynaptic 5-HT input is not necessary for the downregulation of 5-HT$_2$ receptors in animal models [28, 29]. A better understanding of the individual 5-HT receptor changes after chronic antidepressant