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REVIEW

Can we increase speed and efficacy of antidepressant treatments? Part I: General aspects and monoamine-based strategies

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Abstract
Major depressive disorder (MDD) is a severe psychiatric syndrome with high prevalence and socioeconomic impact. Current antidepressant treatments are based on the blockade of serotonin (5-hydroxytryptamine, 5-HT) and/or noradrenaline transporters. These drugs show slow onset of clinical action and limited efficacy, partly due to the activation of physiological negative feed-back mechanisms operating through autoreceptors (5-HT_{1A}, 5-HT_{1B}, α_2-adrenoceptors) and postsynaptic receptors (e.g., 5-HT_3). As a result, clinically-relevant doses of reuptake inhibitors increase extracellular (active) 5-HT concentrations in the midbrain raphe nuclei but not in forebrain, as indicated by rodent microdialysis studies and by PET-scan studies in primate/human brain. The prevention of these self-inhibitory mechanisms by antagonists of the above receptors augments preclinical and clinical antidepressant effects. Hence, the mixed ß-adrenoceptor/5-HT_{1A} antagonist pindolol accelerated, and in some cases enhanced, the clinical action of selective serotonin reuptake inhibitors (SSRI). This strategy has been incorporated into two new multi-target antidepressant drugs, vilazodone and vortioxetine, which combine 5-HT reuptake inhibition and partial agonism at 5-HT_{1A} receptors. Vortioxetine shows also high affinity for other 5-HT receptors, including excitatory 5-HT_3 receptors located in cortical and hippocampal GABA interneurons. 5-HT_3 receptor blockade by vortioxetine enhances pyramidal neuron activity in prefrontal cortex as well as cortical and hippocampal 5-HT release. It is still too soon to know whether these new antidepressants will represent a real

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advance over existing drugs in the real world. However, their development opened the way to future antidepressant drugs based on the prevention of local and distal self-inhibitory mechanisms attenuating monoamine activity.

1. Socioeconomic impact of Major Depressive Disorder

Major Depressive Disorder (MDD) is a severe psychiatric syndrome with very high socioeconomic impact worldwide (Murray et al., 2012; Whiteford et al., 2013). A study from the European Brain Council indicated that brain disorders cost almost 800 billion € per year to European countries (Gustavsson et al., 2011). More than one quarter of this high burden is attributable to psychiatric disorders, including mood and anxiety disorders, which account for 113 billion €, and psychotic disorders, which account for 94 billion €. A recent study by the Global Burden of Disease Study Group indicates that MDD is one of the leading causes of illness-induced disability worldwide. It is the first leading cause of years lived with disability in 56 countries, the second one in another 56 countries and the third one in 34 countries (Global Burden of Disease Study 2013 Collaborators, 2015).

The large impact of MDD is attributable to three main factors. On the one hand, MDD is a highly prevalent disorder in the general population (Kessler et al., 2005, 2007; Phillips et al., 2009; Baxter et al., 2013). On the other hand, depressive episodes have a long duration and appear during active periods of adult life (Ferrari et al., 2013), which results in very large labor costs. Finally, standard MDD treatments are far from optimal, which leaves a high percentage of patients with incomplete responses and poor quality of life, thus increasing suicide risk.

2. Slow and limited action of monoamine-based antidepressant drugs

The limited efficacy of antidepressant drugs is a very important contributor to the large -and possibly increasing- impact of MDD. The treatment of MDD is mainly based on SSRI (Selective Serotonin -5-HT- Reuptake Inhibitors) and SNRI (Serotonin and Noradrenaline –NA- Reuptake Inhibitors), which increase serotonergic and noradrenergic neurotransmission in order to relieve depressive symptoms. A few antidepressant drugs antagonize postsynaptic monoamine receptors with little or no inhibition of the serotonin transporter (SERT), such as agomelatine, mirtazapine, trazodone, nefazodone, etc. SSRI and SNRI are pharmacological refinements of first-generation antidepressant drugs –tricyclic antidepressants (TCA) such as imipramine or chlomipramine- which were discovered by serendipity 6 decades ago when searching for antipsychotic drugs with a chemical structure similar to that of chlorpromazine (the first antipsychotic drug, also discovered by serendipity when searching for sedative agents to potentiate general anesthetics; reviewed in Brown and Rosdolsky (2015) and Ban (2007). The current use of TCA and monoamine oxidase inhibitors (MAOI) is minimal, due to their severe side effects. The development of SSRI -and subsequently, of SNRI- enabled to "clean" antidepressant treatments, removing additional pharmacological activities responsible for the severe side effects of TCAS (blockade of α_1-adrenoceptors, histamine H1receptors, muscarinic receptors, etc.). Moreover, MAOI can cause severe hypertensive episodes when associated with tyramine-containing foods. However, despite that the lack of severe side effects and increased treatment compliance, newer drugs did not surpass the efficacy of some TCA, such as chlomipramine (Danish University Antidepressant Group 1986, 1990).

Clinical trials in research settings with selected patient populations typically yield response and remission rates of ~60% and ~40%, respectively, with standard antidepressant drugs (Tollefson and Holman, 1994; Stahl, 2000; Thase et al., 2001). However, data from naturalistic studies, such as the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) revealed that 80% of MDD patients have recurrent or chronic depression, and that response and remission rates are substantially lower than in research settings (e.g., 47% and 28%, respectively, after a 8-wk treatment with the SSRI citalopram; Trivedi et al., 2006a). Augmentation strategies with drugs not targeting SERT in patients not responding to SSRI yielded similar remission rates (Rush et al., 2006a, 2006b). The STAR*D study also showed that the overall remission rate increased to 67% after four sequenced treatments with different antidepressant drugs during 1 yr (Rush et al., 2006b). These figures from the real world indicate that nearly one third of treated depressed patients do not respond adequately to standard treatments.

An important element of complexity when assessing treatment response is the existence of generic polymorphisms. Hence, polymorphisms of the promoter region of the SERT gene, targeted by SSRI and SNRI, are involved in the clinical response. Homozygotes for the long variant (l/l) and heterozygotes (l/s) showed a better response to SSRI than homozygotes for the short variant (s/s) (Smeraldi et al., 1998; Zanardi et al., 2000; Serretti et al., 2007). Interestingly, the organic cation transporter 3 (OCT3), a high-capacity, corticosterone-sensitive transporter mediating the bidirectional transport of monoamines, may take the role of SERT when this is down-regulated or absent (Baganz et al., 2008). Likewise, an increased expression or function of 5-HT_{1A} autoreceptores -which limit antidepressant effects, see below - is associated to MDD, suicide and poor response to antidepressant drugs (Stockmeier et al., 1998; Lemonde et al., 2003; Neff et al., 2009; Albert et al., 2014). Other genes, not directly related to the mechanism of action of SSRI/SNRI play also important roles, such as polymorphisms of FKBP5, a glucocorticoid receptor-related gene, involved in antidepressant response and recurrence of depressive episodes (Binder et al., 2004).

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