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Faster, better, stronger: Towards new antidepressant therapeutic strategies ☆

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ABSTRACT

Major depression is a highly prevalent disorder and is predicted to be the second leading cause of disease burden by 2020. Although many antidepressant drugs are currently available, they are far from optimal. Approximately 50% of patients do not respond to initial first line antidepressant treatment, while approximately one third fail to achieve remission following several pharmacological interventions. Furthermore, several weeks or months of treatment are often required before clinical improvement, if any, is reported. Moreover, most of the commonly used antidepressants have been primarily designed to increase synaptic availability of serotonin and/or noradrenaline and although they are of therapeutic benefit to many patients, it is clear that other therapeutic targets are required if we are going to improve the response and remission rates. It is clear that more effective, rapid-acting antidepressants with novel mechanisms of action are required. The purpose of this review is to outline the current strategies that are being taken in both preclinical and clinical settings for identifying superior antidepressant drugs. The realisation that ketamine has rapid antidepressant-like effects in treatment resistant patients has reenergised the field. Further, developing an understanding of the mechanisms underlying the rapid antidepressant effects in treatment-resistant patients by drugs such as ketamine may uncover novel therapeutic targets that can be exploited to meet the Olympian challenge of developing faster, better and stronger antidepressant drugs.

1. Introduction

Major depressive disorder is a highly pervasive disorder and is a leading cause of disability worldwide. In the USA alone, major depressive disorder has a lifetime prevalence of approximately 16% and is the largest contributor to lost work productivity (Kessler et al., 2006, 2007, 2008; Kessler and Bromet, 2013). Furthermore, it adversely affects the outcomes of co-morbid medical conditions such as cardiovascular disease, and has also been identified as an independent risk factor for this disease (Benton et al., 2007; Frasure-Smith et al., 2007).

Pharmacological treatments for depression emerged largely through serendipity in the 1950s (Slattery et al., 2004). Today, several classes of antidepressant drugs are currently used for the treatment of depression and although they differ from each other in their relative selectivity for certain transporters or receptors, most of them have been developed with the goal of enhancing serotonergic and/or noradrenergic neurotransmission. The oldest antidepressant drugs include the monoamine oxidase inhibitors (MOAIs) and the tricyclic antidepressants (TCAs). MAOIs inhibit the enzymatic degradation of serotonin, noradrenaline and dopamine thus increasing their availability. On the other hand, TCAs increase synaptic concentrations of serotonin and/or noradrenaline by inhibiting their reuptake by the serotonin and/or noradrenaline transporter, respectively. However, TCAs also have high affinity for several receptors including α_1-adrenoceptors, serotonergic receptors, histamine receptors and muscarinic acetylcholine receptors, and as a result have a large side effect profile. Moreover, MAOIs can have serious adverse effects including the induction of dangerously high blood pressure when taken with certain foods or medications and thus are not the first choice of drug for the treatment of depression. The

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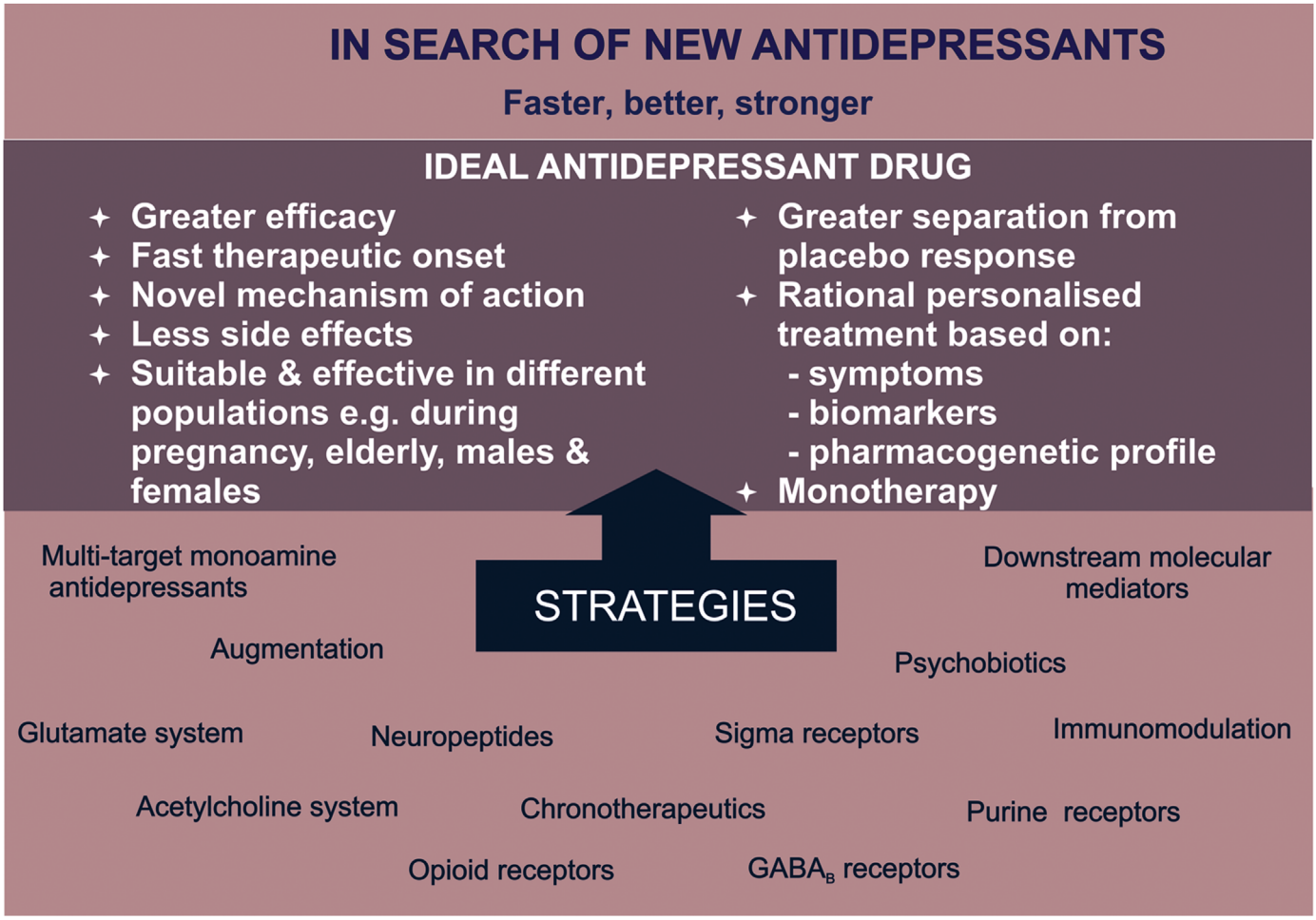

Fig. 1. A schematic summarising the properties of an ideal antidepressant drug, and the current strategies towards achieving this goal.

current first line antidepressant drugs are the selective serotonin reuptake inhibitors (SSRIs) followed by several serotonin and noradrenaline reuptake inhibitors (SNRIs). These contemporary antidepressants have been designed to selectively target the serotonin and/or noradrenaline transporters while having limited direct effects on monoaminergic, muscarinic and histamine receptors, and as a result have a more favourable side-effect profile than the TCAs. However, despite their improved side effect profiles, SSRIs are not more efficacious than the older TCAs (Anderson, 1998, 2000; Millan, 2006). Although today's antidepressant drugs are beneficial for many patients, up to 50% of patients fail to achieve remission with first line antidepressant treatment (Fava, 2003). Indeed, the recent large multi-centre effectiveness trial, Sequenced Treatment Alternatives to relieve Depression (STAR*D), revealed that approximately 47% of patients failed to respond to a first line antidepressant treatment (the SSRI, citalopram), and 1 in 3 did not achieve remission after 4 different consecutive interventions (Trivedi et al., 2006; Warden et al., 2007). The other major problem with our current antidepressant drugs relates to their slow onset of action. Indeed, several weeks or months of treatment are often required before clinical improvement, if any, is reported. Thus, there is a clear unmet medical need for better, stronger and faster-acting antidepressant drugs that have a mechanism of action beyond immediate enhancement of serotonergic and noradrenergic neurotransmission (as summarised in Fig. 1). The present review will outline some of the newer on-going strategies being investigated with a goal towards developing such drugs (as summarised in Fig. 1).

2. Making current antidepressant drug strategies better and stronger: optimisation of monoamine antidepressants

2.1. Multi-target strategies

The rational development of antidepressant drugs that selectively inhibit the serotonin transporter or the noradrenaline transporter has yielded antidepressant drugs with improved side effect profiles, however they have not demonstrated greater efficacy than the older tricyclic drugs (Millan, 2006). Nevertheless, many patients still benefit from these selective reuptake inhibitors and thus much effort has been directed towards to optimising their therapeutic effects. One approach to this has been the rational design of multi-target drugs that selectively target transporters as well as certain monoaminergic receptors, the premise being that these receptors are important for either the mechanism of antidepressant action, limiting adverse side effects, or for treating specific symptoms or co-morbidities such as sleep disruption or anxiety for example (Celada et al., 2013). Indeed, many multi-target antidepressant drugs have now been developed or are currently in development (Connolly and Thase, 2012).

2.1.1. Vilazadone and vortioxetine

Several of these multi-target drugs have been designed to block 5-HT$_{1A/1B}$ autoreceptor function in the hope that this would increase the speed of antidepressant action by relieving the negative feedback