New Antidepressants: New Day or False Dawn?

Luke A. Jelen[1,2] and Allan H. Young[1,2]

1) Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom
2) South London and Maudsley NHS Foundation Trust, London, United Kingdom

Corresponding author: luke.jelen@kcl.ac.uk

Jelen, LA ORCiD: orcid.org/0000-0001-6398-5239
Young, AH ORCiD: orcid.org/0000-0003-2291-6952

Following the introduction of the selective serotonin reuptake inhibitors (SSRIs) from the 1980s onwards, there were no new breakthrough pharmacological treatments for depression until the turn of the millennium. This changed with the serendipitous discovery that a single sub-anaesthetic dose of the dissociative ketamine, a N-Methyl-D-Aspartate (NMDA) glutamate receptor antagonist, could induce rapid and significant reductions in depressive symptoms; a finding since replicated in numerous clinical studies in treatment-resistant unipolar and bipolar depression (Jelen and Stone, 2021). This has taken depression research away from a focus on targeting deficits in monoaminergic neurotransmission towards an exploration of alternative biological targets, including the glutamatergic and GABAergic systems, as promising avenues for next-generation treatments.

Building on evidence for the rapid antidepressant effects of ketamine, investigators have explored whether alternative NMDA receptor antagonists may share ketamine's antidepressant properties, however clinical studies of several other NMDA receptor antagonists and NMDA receptor site modulators (e.g., memantine, GLYX-13, CERC-301) have failed to produce convincing results. More promise has been seen with dextromethorphan-bupropion (AXS-05), an oral NMDA receptor antagonist and sigma-1 receptor antagonist, with a recent phase 3 study demonstrating rapid, substantial, and statistically significant improvement in depressive symptoms and induction of remission (Iosifescu et al., 2022). A new drug application for AXS-05 for the treatment of major depressive disorder (MDD) is under review by the US Food and Drug Administration (FDA).

Meanwhile, the clinical use of ketamine itself has continued to grow. Although racemic (R-S)-ketamine for depression remains an off-label treatment, an (S)-ketamine (esketamine) nasal spray, has been developed and approved for use in treatment-resistant depression (TRD) in the United States and Europe but may only be administered in medically supervised settings. The need for monitoring is important as ketamine has known abuse potential and produces notable side-effects including blood pressure changes, dissociative and cognitive effects. The FDA also approved the use of nasal esketamine for adults with MDD presenting with acute suicidal ideation and behaviour, while the European Medicines Authority has approved its use in situations deemed a psychiatric emergency, to

reduce depressive symptoms rapidly. However, there is still limited guidance on why, when, and how to use esketamine in patients with depression to treat a crisis (Lengvenyte et al., 2022). Although the development of nasal esketamine has brought some standardization to the clinical use of ketamine, alongside a centralised safety monitoring system, there are increasing numbers of unregulated ketamine clinics globally that typically administer off-label (R,S)-ketamine intravenously. Many in the field have urged caution with the use of ketamine, citing concerns with regards to long-term efficacy and safety, highlighting the need for longer-term studies to understand the optimal mode of administration to achieve sustained antidepressant effects and to better characterise side-effects associated with prolonged use (Schatzberg, 2019; McIntyre et al., 2021).

In parallel to its clinical application, ketamine has been used as a tool to probe antidepressant mechanisms in the hope to uncover new targets to aid in the development of rapid-acting antidepressants that may lack ketamine's side-effects and abuse potential. Increasing preclinical evidence suggests that activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and subsequent increase in synaptic plasticity plays a critical role in ketamine's antidepressant mechanism (Jelen et al., 2021). Additional work suggests that ketamine's other enantiomer, (R)-ketamine, and its metabolite (2R,6R)-HNK, appear to stimulate the AMPA receptor, independent of NMDA receptor inhibition. Furthermore, it has been proposed that (R)-ketamine and (2R,6R)-HNK have the potential for more potent and longer-lasting antidepressant effects than (S)-ketamine alongside less behavioural effects and abuse liability (Jelen et al., 2021). While early clinical data suggests (R)-ketamine may produce rapid antidepressant effects without significant dissociation (Leal et al., 2021), findings from definitive clinical trials of (R)-ketamine and 2R,6R)-HNK are awaited.

Aside from ketamine's effects on the excitatory glutamatergic system, ketamine also has direct initial effects on GABAergic interneurons that is hypothesised to drive a surge in glutamate release, AMPA activation and ensuing wave of synaptogenesis. Importantly, ketamine-induced synaptic responses restore GABA inhibitory, as well as glutamate neurotransmission, which may restore balance between inhibitory and excitatory synaptic transmission. Another novel antidepressant drug, brexanolone, an intravenous formulation of the endogenous neurosteroid allopregnanolone, has emerged that acts to enhance GABAergic transmission directly. Brexanolone, delivered as a 60 hour infusion, has demonstrated antidepressant efficacy in females with post-partum depression (PPD) across phase 2 and phase 3 studies, and was associated with a rapid onset of action (within 60 hours) with durable responses sustained up to 30 days after the infusion (Meltzer-Brody et al., 2018). Brexanolone subsequently became the first drug approved for post-partum depression by the FDA in 2019. Unfortunately, significant barriers to widespread use include its complex means of administration (60 hours continuous infusion with monitoring due to risks of syncope and sedation) and high estimated

costs (single course of treatment around $34,000). Zuranolone is a neuroactive steroid GABA-A positive allosteric modulator, has been developed as a potential improvement to brexanolone, with high oral bioavailability and half-life for once-daily administration. In phase 3 trials, zuranolone 50 mg once-daily for two-weeks demonstrated a statistically significant and clinically meaningful improvement in depressive symptoms at day 15 in both MDD (Biogen, 2021) and PPD (Biogen, 2022).

Besides the focus on glutamatergic and GABAergic mechanisms, there been a resurgence of interest in the therapeutic potential of acutely modulating the monoamine system with classic psychedelics (drugs with serotonin 2A receptor agonist properties that can produce changes in perception, mood, and cognition), with promising early results in a range of psychiatric conditions, including psilocybin for major depressive disorder (Carhart-Harris et al., 2021; Rucker et al., 2018). In 2018 the FDA granted breakthrough therapy designation to psilocybin and a large multicenter phase 2B trial investigating psilocybin with psychological support for TRD has recently been completed. There was a rapid onset of action and durable effects with treatment differences between the 25 mg vs 1 mg group apparent from the day after psilocybin administration, with a difference of -6.6 points in change from baseline MADRS total scores at week 3 ($p<0.001$) (Compass Pathways PLC, 2021). Public and industry excitement surrounding psychedelics has been increasing in recent years with a growing wave of commercial investment in the hope that these compounds will be a 'game-changer' for psychiatric conditions including depression. Despite early promising results it is important to highlight some of the challenges in delivering and interpreting findings from these studies. Psychedelic studies are likely to significantly overestimate treatment effects by design due to unblinding (profound psychoactive effects) and expectancy effects (participants are likely to have come across portrayals of psychedelics which claim the substances are highly effective, leading to positive expectation) (Aday et al., 2022). Additionally, clinical psychedelic studies usually administer the drugs alongside psychological support, and it is therefore difficult to disambiguate the drug's 'true' pharmacological effect.

To conclude, research over the last two decades has ushered a new era of considerable hope regarding our ability to develop better treatments for individuals with depression. Beyond the monoamine system, ketamine and brexanolone have emerged as novel rapid-acting antidepressants with completely new mechanisms of action. However, despite intranasal esketamine and brexanolone receiving licenses for the treatment of TRD and post-partum depression respectively, there are ongoing debates with regards to cost-effectiveness, deliverability, and in ketamine's case, particular concerns regarding longer-term efficacy, safety, and abuse liability. Meanwhile, psychedelic drugs including psilocybin have become the next blockbuster hope for depression. While early results are promising, the field must maintain equipoise and temper hype as larger studies are completed. Only time will tell if this is the start of a new day or false dawn in the treatment of depression.

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