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ACCEPTED MANUSCRIPT

The development of glutamate-based antidepressants is taking longer than expected

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During the 1990s, multiple preclinical studies demonstrated that *N*-methyl-D-aspartate receptor (NMDAR) antagonists can produce rapid-onset antidepressant-like effects in rodents [1]). In 2000, a pilot study reported that intravenous infusion of a subanesthetic dose (0.5 mg/kg) of the NMDAR antagonist ketamine (0.5 mg/kg) produced a rapid and robust antidepressant effect in patients with depression [2]. These observations raised the possibility of an alternative to available biogenic amine-based antidepressants that often take weeks to months to produce a clinically meaningful therapeutic effect, leaving patients at increased risk of suicide [1,3,4].

Between 15% and 30% of patients who have a major depressive disorder (MDD) do not respond satisfactorily to two successive courses of antidepressant treatment ('treatment-resistant depression'; TRD) [1,3,4]. In 2006, a randomized controlled trial (RCT) conducted by the National Institute of Health (NIH) [5] clearly demonstrated a rapid and robust effect of subanesthetic ketamine in TRD. This study was a milestone because of the profound impact of TRD on public health: patients with TRD experience a reduced quality of life, severe impairment in social functioning and workplace performance, and are at increased risk of suicide, all contributing to a significant healthcare burden [1,3,4]. Although growing in popularity, the use of intravenous subanesthetic ketamine in TRD remains off-label, limited to a medical setting, and is burdened by other significant challenges [3]. Perhaps most importantly, the psychodysleptic (and, to a lesser extent, abuse) liabilities of ketamine require close supervision. Moreover, the place of ketamine among current treatment strategies remains unsettled, particularly its use in patients who are suicidal.

Over the past decade, an increasing number of glutamate-based antidepressants have been studied, with few successes and frequent disappointing results. Here, we propose alternative clinical trials, with the aim to reinvestigate and/or accelerate the clinical development of these novel compounds.

Phase II clinical trials with selective NR2B NMDAR antagonists: negative data or failed studies?

Ketamine is a nonselective NMDAR channel blocker [1]. In an effort to maintain its robust antidepressant effects and avoid the psychotomimetic adverse effects of ketamine and other channel blockers, investigators initially pursued NR2B-subtype NMDAR antagonists. Phase II trials with NR2B-subtype selective antagonists have generally been viewed as disappointing [3,4,6]. Despite positive Phase II data in patients who did not respond adequately to at least one course of treatment with a selective serotonin reuptake inhibitor (SSRI) [7], the development of traxoprodil (CP 101,6060; ClinicalTrials.gov identifier: NCT00163059, traxoprodil also has sigma-1 effects) was halted because of QT prolongation, whereas that of oral EVT-101 (Janssen R&D, USA, Evotec, Germany and Hoffmann-La Roche, Switzerland; NCT01128452) was not completed because of recruitment difficulties. A third NR2B NMDAR antagonist, rislenemdaz (formerly MK-0657, CERC-301, Cerecor, USA; NCT01941043 and NCT02459236) failed to show clinically significant antidepressant efficacy in two cohorts of patients with TRD. Although there were hints of efficacy in several reports, the low-trapping NMDAR channel blocker, lanicemine (AZD6765, Astra-Zeneca, UK), lacked clinically significant antidepressant efficacy (NCT00986479).

Given both the antidepressant signal and the accompanying dissociative effects (resulting in a dose reduction in subsequent cohorts) seen with traxoprodil, the failure of other selective NR2B NMDAR antagonists and lanicemine to produce ketamine-like antidepressant effects could result from investigated doses that were too low [6]. Thus, the dissociative effects produced by ketamine and traxoprodil might represent a crude measure of target engagement (i.e. NMDAR blockade sufficient to evoke a pharmacological effect), whereas dissociative effects were not reported with either these other NR2B antagonists or lanicemine. To test this hypothesis (and potentially resuscitate shelved molecules), the appearance of dissociative-like symptoms in dose-escalation studies using

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