Published in final edited form as:

Drug Discov Today. 2018 October ; 23(10): 1689–1692. doi:10.1016/j.drudis.2018.02.006.

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

Ricardo Garay,

¹Department of Pharmacology and Therapeutics, Craven, Villemoisson-sur-Orge, France

²CNRS, National Centre of Scientific Research, Paris, France ricardo.garay@orange.fr

Carlos A. Zarate,

Experimental Therapeutics and Pathophysiology Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA

Icilio Cavero,

Department of Safety Pharmacology, Craven, Villemoisson-sur-Orge, France

Yong-Ku Kim,

Department of Psychiatry, College of Medicine, Korea University, Seoul, Republic of Korea

Thomas Charpeaud, and

Centre Médico-Psychologique B, CHU, Université d'Auvergne, Clermont-Ferrand, France

Phil Skolnick

Opiant Pharmaceuticals, Santa Monica, CA, USA

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

Conflicts of interest

R.P.G. is the president and I.C. a member of Craven (Villemoisson-sur-Orge, France), a nonprofit association for therapeutic innovation. C.A.Z. is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation, on a patent for the use of (2R,6R)-hydroxynorketamine, (S)-dehydronorketamine, and other stereoisomeric dehydro- and hydroxylated metabolites of (R,S)-ketamine metabolites in the treatment of depression and neuropathic pain, and on a patent application for the use of (2R,6R)-hydroxynorketamine and (2S,6S)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and post-traumatic stress disorders. C.A.Z. has assigned his patent rights to the US Government, but will share a percentage of any royalties that might be received by the Government. T.C. declares consultant activities and conferences for Astra-Zeneca, BMS, Janssen, Lundbeck, and Otsuka; invitation to Congress by Janssen, Lundbeck, and Otsuka; and research activities for AMGEN, Janssen, and Lilly. Over the past 36 months. P.S. has been a full-time employee of Opiant Pharmaceuticals, Inc..

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; [Clinical-Trials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00163059) 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 normal volunteers could identify

suitable doses for Phase II studies. In these Phase II studies, ketamine could be used as a positive comparator in either a parallel arm of crossover design.

Another possibility is that ketamine or traxoprodil act by off-site effects that are beyond the NMDAR.

Is NMDAR inhibition the only antidepressant mechanism of ketamine?

The mechanism of action of ketamine is complex and not fully understood [4]. Ketamine has also been reported to inhibit catecholamine reuptake and interact with several other central nervous system targets, including opioid, sigma, and muscarinic receptors [3,4]. However, a low affinity of ketamine for these receptors relative to NMDARs indicates that target engagement is unlikely at the subanesthetic doses of ketamine producing rapid and robust antidepressant actions.

Recent preclinical studies indicate that the antidepressant effects of ketamine might involve, at least in part, additional or different downstream effects that might not be shared by other NMDAR antagonists [4]. In particular, the antidepressant-like effects of racemic ketamine are accompanied by early and sustained α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (AMPA) activation, which was attributed to the R-ketamine metabolite (2R, 6R-hydroxynorketamine). Additional pharmacological targets might emerge from ongoing pre-clinical studies aimed at elucidating the downstream actions of ketamine, including effects at other glutamatergic receptors, signaling pathways (BDNF–TrkB signaling) and effectors (synapto-genesis in the prefrontal cortex, dentate gyrus, and CA3 region of the hippocampus) [4,8]. Results from preclinical studies [1] have already led to the clinical testing of other glutamatergic modulators, such as the metabotropic glutamate receptor (mGluR) modulator basimglurant (NCT02433093), the AMPA potentiator Org 26576 (NCT00610649), and the mGlu2/mGlu3 modulator RO4995819 [3,4]. Although Phase II data with these compounds have been disappointing, factors such as the inability to determine appropriate dosing to achieve target engagement for many of these molecules demonstrate the need for better molecular probes. Without better tools to assess target engagement, it is unlikely that clinical development of such compounds can proceed.

Late-stage clinical development of esketamine

Intranasal esketamine (Janssen R&D, USA) exhibited antidepressant effects in Phase II trials and is now being assessed in Phase III studies as a potential adjunctive treatment in TRD therapies (Table 1) [3,8]. Esketamine, the S-enantiomer of ketamine, has three-fourfold higher affinity for NMDAR and greater general anesthetic potency than the R-enantiomer (arketamine). Positive results were obtained in Phase II clinical trials with an injectable (NCT01640080) and an intranasal formulation of esketamine (NCT01998958, NCT02133001). In November 2013, the US Food and Drug Administration (FDA) granted Breakthrough Therapy Designation (BTD) to intranasal esketamine for MDD with imminent risk for suicide. Intranasal esketamine is now completing Phase III development in TRD, with estimated primary completion dates between June 2017 and April 2018 (Table 1).

Is S-ketamine superior to R-ketamine?

There are no ongoing clinical trials directly comparing the antidepressant efficacies of the two ketamine enantiomers. In several rodent models of depression, R-ketamine exhibited higher potency and longer lasting antidepressant-like activity than the S-enantiomer (esketamine), although the latter has a fourfold higher affinity for NMDAR [8]. Moreover, S-, but not R-ketamine, produces psychotomimetic-like behavioral effects in rodents [8] and, in ten healthy male volunteers, S-ketamine was reported to produce milder subjective adverse effects than R-ketamine [9]. Ideally, a study directly comparing these enantiomers (at comparable doses) could help to establish their adverse effect profile and determine whether there are potential therapeutic advantages in TRD. Finally, the contribution of other nonglutamatergic offsite targets to the efficacy needs to be evaluated.

The next 5 years

In addition to intranasal esketamine, rapastinel (formerly GLYX-13, Allergan, USA) is also ongoing late-stage clinical development in TRD [10] (Table 1). Rapastinel is a synthetic peptide described as a glycine B-like functional partial agonist, binding to the glycine allosteric site of NMDAR [10]. Following a successful Phase II clinical trial (NCT01234558, see also NCT01684163), intravenous rapastinel received BTB from the FDA. The sponsor initiated Phase III development in October 2016, with primary trial completion date expected to be between November 2018 and February 2020 (Table 1).

The value of NMDARs as targets for antidepressant development will be more clearly defined when results from ongoing Phase III studies with esketamine and rapastinel are available. Moreover, AV-101 (VistaGen, USA), an antagonist acting at the glycine site on NMDAR, is currently being evaluated in Phase II trials (NCT03078322, NCT0248445) with a primary completion date between March and December 2019 [3]. Phase II trials are also underway with nonselective NMDAR antagonists AVP-923 (NCT01882829) and AVP-786 (NCT02153502).

Concluding remarks

Intranasal esketamine and intravenous rapastinel are now being assessed in Phase III studies, thus raising hopes for the regulatory approval of rapidly acting, robust, and sustained glutamatergic antidepressants within the next 5 years. Clinical studies comparing both ketamine enantiomers would be desirable based on preclinical data demonstrating that R-ketamine exhibited a higher potency and longer lasting antidepressant-like activity compared with S-ketamine, although the latter is four times more potent at NMDAR. Selective NR2B NMDAR antagonists and traxoprodil should also be re-investigated in TRD, using doses that, similar to ketamine, provide some indication of target engagement. Finally, preclinical and clinical research continue to both reveal and better define potential molecular events produced by ketamine and related agents that have the potential to evolve into novel targets for developing breakthrough therapies for depression.

References

1. Skolnick P et al. (2009) Glutamate-based antidepressants: 20 years on. *Trends Pharmacol. Sci.* 30, 563–569 [PubMed: 19837463]
2. Berman RM et al. (2000) Antidepressant effects of ketamine in depressed patients. *Biol. Psychiatry* 47, 351–354 [PubMed: 10686270]
3. Garay RP et al. (2017) Investigational drugs in recent clinical trials for treatment-resistant depression. *Expert Rev. Neurother.* 17, 593–609 [PubMed: 28092469]
4. Zarate CA, Jr and Machado-Vieira R (2017) Ketamine: translating mechanistic discoveries into the next generation of glutamate modulators for mood disorders. *Mol. Psychiatry* 22, 324–327 [PubMed: 28070122]
5. Zarate CA, Jr et al. (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch. Gen. Psychiatry* 63, 856–864 [PubMed: 16894061]
6. Skolnick P et al. (2015) Effect of NMDAR antagonists in the tetrabenazine test for antidepressants: comparison with the tail suspension test. *Acta Neuropsychiatr.* 27, 228–234 [PubMed: 25858023]
7. Preskorn SH et al. (2008) An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. *J. Clin. Psychopharmacol.* 28, 631–637 [PubMed: 19011431]
8. Yang C et al. (2015) R-ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects. *Transl. Psychiatry* 5, e632 [PubMed: 26327690]
9. Persson J et al. (2002) Pharmacokinetics and non-analgesic effects of S- and R- ketamines in healthy volunteers with normal and reduced metabolic capacity. *Eur. J. Clin. Pharmacol.* 57, 869–875 [PubMed: 11936706]
10. Moskal JR et al. (2017) The development of rapastinel (formerly GLYX-13); a rapid acting and long lasting antidepressant. *Curr. Neuropharmacol.* 15, 47–56 [PubMed: 26997507]

TABLE 1
Phase III clinical trials with intranasal esketamine and intravenous rapastinel for treatment-resistant depression^a

Compound	Identifier ClinicalTrials.gov	Sponsor's	Primary outcome	Time frame	N ^b	Primary completion date ^c
Esketamine	NCT02417064	TRANSFORM-1	MADRS ^d	4 W	348	April 2018
	NCT02418585	TRANSFORM-2	MADRS ^d	4 W	236	June 2017
	NCT02422186	TRANSFORM-3	MADRS ^{d,e}	4 W	139	August 2017
	NCT02493868	SUSTAIN-1	Time to relapse ^f	104 W	333	April 2018
	NCT02497287	SUSTAIN-2	Safety	56 W	750	October 2017
Rapastinel	NCT02932943	RAP-MD-01	MADRS ^d	1 D	700	November 2018
	NCT02943564	RAP-MD-02	MADRS ^d	1 D	1050	December 2018
	NCT02943577	RAP-MD-03	MADRS ^d	1 D	700	December 2018
	NCT02951988	-	Time to relapse ^f	52 W	600	September 2019
	NCT03002077	-	Safety	52 W	500	February 2020

^a Abbreviations: D, days; MSDRS, Montgomery-Asberg Depression Rating Scale; W, weeks.

^b Number of enrolled patients (final or estimated).

^c Past or estimated.

^d Change from baseline in MSDRS.

^e Older subjects.

^f Time to relapse in patients with stable remission.