

PARTNER PERSPECTIVES

Exploring the Potential of an Investigational NMDAR Channel Blocker for Major Depressive Disorder

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People living with major depressive disorder (MDD) often experience a measure of symptom relief with current first-line options, but notable treatment needs remain, such as improvement of residual symptoms, fewer adverse effects, and more rapid onset of therapeutic effect. Several agents for the treatment of MDD are in development, including REL-1017, a novel *N*-methyl-D-aspartate receptor (NMDAR) channel blocker.

In this interview, **Marco Pappagallo, MD**, chief medical officer of Relmada Therapeutics, Inc, shares insight regarding the investigation of REL-1017 and its potential role in the treatment spectrum. He previously served as Professor and Director of Pain research in the Department of Anesthesiology, at Mount Sinai Medical Center in New York City, holds 4 patents for novel nonopioid analgesic approaches to chronic pain, and has edited and authored 4 textbooks and more than 100 articles in peer-reviewed journals.

Could you talk about your role at Relmada Therapeutics Inc as a pain management specialist, active clinician, and published author?

I have been a Chief Medical Officer before and enjoyed how my clinical experience has helped guide drug development and other aspects of the complex process of advancing an investigational program toward FDA submission and approval.

As a pain management specialist who continues to see patients in the clinic, I see the burden of depression quite a bit. As a person with friends and family members affected by mental illnesses, I am also aware of the burden and suffering that depression continues to inflict on people and of the need for more effective treatment options and innovation in the fight against depression. I am very motivated and grateful to be part of bringing a novel therapy forward.

I would also add that the pharmacology of REL-1017 relates to mechanisms that we know well in pain management: NMDAR and racemic methadone.

How would you characterize the current treatment spectrum and unmet needs for patients with MDD?

There is a very large number of approved drugs for depression, yet both

clinicians and patients recognize the limitations of today's therapies and the need for additional options. In terms of efficacy, as demonstrated by the STAR*D trial, more than half of patients treated with antidepressants continue to experience meaningful symptoms of depression. Delayed onset is an additional limitation, with current treatments taking 4 to 8 weeks to work—when they work. We also hear from clinicians, patients, and the advocacy community about burdensome adverse effects affecting long-term adherence and overall quality-of-life, such as sexual dysfunction and weight gain. In terms of adjunctive treatments for MDD, there are currently only 3 options approved by the FDA, all of which are atypical antipsychotics with neurological and metabolic adverse effects. A safe, well-tolerated treatment option that is effective and works quickly could mean a great deal to patients and their families.

What should clinicians know about the investigational drug REL-1017 before considering referring patients or participating as an investigator site?

REL-1017 is a novel NMDAR channel blocker. REL-1017 is thought to work through a selective, preferential block of abnormally hyperactive channels associated with depression while avoiding

effects on channels that are associated with normal physiological functions. New data indicate that this unique activity may be related to its preference for NMDARs containing the GluN2D subunit, specifically. With this mechanism, REL-1017 is being evaluated to determine whether it can provide therapeutic effectiveness for patients with depression without the psychotomimetic effects or other cognitive adverse effects that have limited the clinical utility of other NMDAR channel blockers, such as ketamine or MK-801.

The molecule itself is esmethadone, the opioid-inactive dextro-isomer of methadone. It is also referred to as dextro- or d-methadone. It is a new chemical entity NCE and is pharmacologically distinct from both the parent racemate—ie, methadone—as well as the levo-isomer of methadone, or l-methadone, which are powerful opioids. In contrast, esmethadone's lack of clinically significant opioid agonistic effects enables the potential for antidepressant activity without the risk of addiction and respiratory depression of methadone.

The therapeutic potential of esmethadone was first identified and explored at New York Presbyterian/Weill Cornell Medicine. Researchers observed that when esmethadone was tried in late-stage cancer patients, their pain did not improve but there were positive effects on mood. In parallel, we were learning more about the NMDAR's role in depression. Since then, phase 1 and 2 studies have supported esmethadone's continued development as a potentially safe, effective antidepressant with quite rapid onset. However, these very encouraging results need to be further confirmed in larger and longer phase 3 studies. Relmada Therapeutics, Inc is currently conducting these studies as part of our RELIANCE Clinical Research Program.

What should psychiatrists know about the design of the RELIANCE program in MDD?

We are enrolling! The RELIANCE Clinical Research Program is designed to evaluate the potential for REL-1017 as a treatment for MDD. It includes studies assessing the investigational drug as an adjunctive treatment as well as monotherapy. The program includes randomized placebo-controlled studies with a treatment phase of 28 days, which can be followed by a long-term, open-label safety study in which all participants receive REL-1017, the investigational drug.

In all placebo-controlled studies in the RELIANCE Clinical Research Program, participants have a 1:1 ratio, or a 50/50 chance of receiving a placebo during the 28-day treatment phase. All participants in the placebo-controlled studies will have the option to roll over into RELIANCE-OLS, the long-term, open-label safety study in which all participants receive REL-1017. The duration of RELIANCE-OLS is at least 1 year and the study will also include people who enroll directly, without previous RELIANCE trial participation.

These studies are being conducted at clinical trial sites throughout the United States. COVID-19 has propelled us toward virtual clinical trials, reducing the logistical and transportation burden for participants.

We will continue recruiting throughout 2021 with the goal of completing our 2 pivotal adjunctive treatment studies in the first half of 2022.

Can you share more details about the design of the program—specifically, eligibility criteria and outcome measures?

This program was designed by leading experts in the field of depression, including Dr Maurizio Fava of Harvard Medical School and Massachusetts General Hospital. We are very grateful for his expertise, as well as that of our many great scientific advisors.

The primary end point in these studies is a standard scale accepted by the FDA for evaluation of treatments for MDD: the MADRS [Montgomery-Asberg Depression Rating Scale] at day 28. We expect rapid efficacy, and therefore the change in MADRS at day 7 is a key secondary end point; we are also capturing several different parameters, including quality-of-life measures.

The studies are devised for adults, and the inclusion and exclusion criteria are standard for these types of clinical trials. We are also considering an approach for adolescents and younger children. We welcome interest from your readers.

How do you see an agent such as REL-1017 potentially fitting into the current treatment landscape in MDD?

Our primary focus is the phase 3 program to support [a new drug] application to the FDA for REL-1017 as an adjunctive treatment for MDD.

We see the opportunity to pursue the adjunctive indication as important for several reasons. First, many patients do have some benefit from their first-line therapies and may not want to discontinue therapy but would appreciate an additional option that could help. Second, as clinicians, we appreciate that the weaning off of these medications is not trivial, and doing so can delay the progress towards benefiting from therapy. Lastly, there have only been 3 antidepressant drugs approved by the FDA to date as adjunctive treatments, all of which are atypical antipsychotic agents. Thus, there is a real opportunity to provide a novel therapeutic option as an adjunctive treatment.

If a clinician or a patient is interested in learning more about the program or this investigational agent, what is the best way they can get in contact?

Please do reach out, whether you are interested as an investigator, on behalf of potential patient participants, or because of a loved one who may be interested. We are actively talking to clinicians about setting up clinical trial sites and operations around the United States but are always open for discussions and inquiry.

Please email us at clinicaltrials@relmada.com.