This is the podcast for the journal Neuropsychopharmacology, I’m Cynthia Graber.

Historically, anti-depressants have acted fairly slowly. Onset of action can take a couple of weeks, even months.

SM: So there's been a lot of interest over the last 20 plus years in developing drugs that work relatively quickly. And by that we mean generally have an onset of action within a week. So instead of several weeks, within seven days or even earlier.

Sanjay Mathew is a professor and vice chair for research at Baylor College of Medicine and director of the Mood and Anxiety Disorders Program. He’s one of the two authors of a recent review paper in the journal Neuropsychopharmacology, “The why, when, where, how, and so what of so-called rapidly acting antidepressants.” With his colleague Alan Schatzberg, professor of psychiatry and behavioral sciences and director of the Mood Disorders Center at Stanford University, they explore both the drugs that have been studied as rapidly-acting anti-depressants to date, and they also review the challenges and opportunities in how such research is conducted. They say that a version of ketamine has changed the field.

AS: Ketamine has been a game changer, I think, in that the administration of ketamine has been associated with rather rapid improvement in depressed mood in patients who are, have largely been refractory to treatment, who have not shown responses to traditional treatments or partial responses. So it has been a dramatic step forward in terms of being able to effect a relatively rapid relief for people suffering from the disorder. And it has led to lots of research, lots of debates, lots of questions, but it's become not only a leader of the field, but a kind of a standard for whether you can in fact develop rapidly acting antidepressants.

So before we get into some of the challenges you both have found with how research is conducted into rapidly-acting anti-depressants, what are some treatments that have shown promise?

SM: The ketamine story's been the most prominent, but there's a lot of other recent examples, including what we talk about in the paper with zuranalone, which is a GABA modulator that was recently approved for postpartum depression.

AS: Some of the other drugs include s-methadone, which is an anteomere (SP?) for methadone that's commonly used in treatment of substance use disorders. There is a combination of dextromethorphan with bupropion that we talk about in the paper. So there are a number of agents that seek to get approval as antidepressants and have some hope that they'll have something that designates them as rapidly acting.

SM: And I should mention, we also talk in the article about beyond drugs, a neuromodulation therapy called Saint, or the SNT, the Stanford Neuromodulation Therapy Platform, which essentially tries to condense six weeks of transcranial magnetic stimulation into five days. And the results were very rapid, what you'd see with a ketamine-like effect.

Let’s talk about some limitations you’ve seen in trials that point to changes you think should be made in terms of how scientists study these kinds of rapidly-acting anti-depressants. We can’t cover everything you raise in the review, but for some highlights, let’s start with the issue of time.

AS: First of all, we need to be thoughtful about what is rapidly acting. You know, is it seven days? Is it three days? Is it one hour? And different drugs kind of report onset of activity in varying lengths of time, some much faster than others, obviously. Some being just a few days, and some being a few hours even. I think that is one question that really needs to be thought of by the field is what is rapidly acting. And in that context, we did raise another point, which is the so-what part of the title of the paper. So what if it's rapidly acting? I mean, if it doesn't last, how much value is that in a disorder that is frequently chronic and long lasting? So that's one issue I think that needs to be addressed.

SM: We have to remember that these are generally highly refractory patients who come into these studies. They've had perhaps 20 years of illness, recurrent episodes. They've had perhaps suicide attempts, hospitalizations, and so on. And so giving them relief for a period of a week - but if they have a sudden relapse, really what is the long-term utility of that approach? Have we really done the patient a service, and is that what we’re aiming here. We would make the argument that’s not what we’re aiming for at all. It would really be resolution of the chronic condition with some kind of maintenance strategy that has to be in place, beyond this quick fix.

And now, how about the question of patient selection, what can and should change there in terms of research?

SM: With respect to the patient selection issue, I think we make the point that the studies that are geared towards finding a rapid antidepressant really have to select the patients for whom this would be of most concern and of most value. And who are those patients? Are they the patients with lower grade depression that are chronic, but they don't really get into trouble or they're not functionally impaired?

We would argue that you have to study it in patients who are most at need for a rapid antidepressant effect. And that those would be patients with suicidal ideation, really poor functioning, or socially disabled, have perhaps some comorbidities that make it much more difficult to treat. And so you have to select the right population first and foremost, which have to be severe.

And often patients with suicidal ideation are excluded from antidepressant trials. And the FDA has actually even made recommendations recently that the inclusion criteria should include these patients who are probably the most deserving of these kind of novel interventions.

Another challenge is measuring the outcomes of any study. What are some of the issues you’ve seen?

SM: It's important to recognize that the scales that we use in depression outcome studies, the MADRS, the Hamilton, these are very old scales, and the timeframe classically is a seven-day lookback. So when you're studying a 24-hour outcome and so on, you're essentially trying to condense the seven-day lookback into 24 hours. But then there are some items that just simply won't be relevant, such as changes in appetite, and even the sleep items can be problematic to look at. And so there's a need for the field to develop more sensitive tools, either digital tools or other types of measures. And there's work in this area that's ongoing, but the field really needs to standardize this in a more rigorous manner.

There are other issues you bring up in your review, such as dose response, and biomarkers. But overall, from your review of the literature, what are some of your big-picture takeaways?

SM: It is a complex, rapidly moving area, both from a regulatory perspective as well as a clinical trials perspective. I think what one of the reviewers made the note that although we've been talking, this is a relatively recent thing, you actually can hail back to the eighties of the work with IV clomipramine as some of the early work developing rapid antidepressants, and reminded us that this work has been going on for a long time, and there have been any number of reasons that it's been challenging to develop this in practice.

AS: Because in the end, we want enduring responses, that are well tolerated and highly effective.

SM: Yeah. I would say rapid and durable is, is what we're after. Because if you rapid but not durable, then, then it gets to the so-what question.

CG: This is the podcast for the journal Neuropsychopharmacology. To read the paper discussed in the podcast, go to [www.nature.com/npp](http://www.nature.com/npp). I’m Cynthia Graber.