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Letter to the Editor

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Response to the letter entitled "Tachyphylaxis and Desensitization Depression" by Richard Skaff

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In Reply:

I appreciate Dr. Skaff's thought-provoking comments about my 2017 *CNS Spectrums* review paper. I agree with his appraisal that the term Treatment Resistant Depression (TRD), especially when operationally defined as nonresponse to 2 adequate trials of medications with established antidepressant effects in the current episode, obscures important differences in both the natural histories and treatment courses of individuals with depressive disorders. I also share Dr. Skaff's belief that someone who becomes persistently depressed after a period of apparent response/remission/recovery on a particular medication may indeed be suffering from a different pathophysiological variant of the illness than someone who has never obtained an adequate response to any form of antidepressant therapy. Like Dr. Skaff, I see patients for whom antidepressants appear to "poop out" and, to try to make sense of this, I sometimes use the term "tachyphylaxis" to describe this phenomenon. However, I am not confident that this clinical state results from a specific pathophysiology ("desensitization depression"). In fact, as I argued in another *CNS Spectrums* review paper over a decade ago, I believe that the most important factor underlying antidepressant "tachyphylaxis" in everyday practice is a fading of the so-called placebo effect. Simply said, if the nonspecific underpinnings of treatment response account for more outcome variance than specific pharmacological effects, maybe the infrequent clinical contact and diminution of therapeutic support that routinely occur during longer term pharmacotherapy have more to do with the loss of therapeutic effect than counter-adaptive receptor changes. Nevertheless, I fully agree with Dr. Skaff that this vexing state warrants careful, systematic study. But, answering the questions about apparent tachyphylaxis may not be easy. We set out to do just this as secondary aim of a large-scale collaborative study that examined outcomes of patients with recurrent Major Depressive Disorder across acute, continuation, and maintenance phases of pharmacotherapy.[1] In that trial, we could not identify any distinctive temporal or symptomatic characteristics that differentiated cases of apparent tachyphylaxis (ie, relapse/recurrence on active medication) from the relapses/recurrences that occurred after patients were switched from active drug to double blind placebo.

The *CNS Spectrums* paper that caught Dr. Skaff's attention was written more than a year before the regulatory fates of esketamine, rapastinel, and the buprenorphine/samidorphan combination had been determined. It is noteworthy that, circa 2017, understanding of the glutamatergic and opiate mechanism(s) of action of these medications had raised concerns about the more classical notion of tolerance of therapeutic effects, namely the one that is linked to drugs with abuse liability and might necessitate pharmacotherapists to use escalating doses to "chase" a waning therapeutic effect. Subsequent research has yielded largely reassuring results about longer term treatment with esketamine[2] and buprenorphine/samidorphan combination,[3] although to date only esketamine has received approval from US Food and Drug Administration. Although tolerance may not commonly develop during ongoing treatment with esketamine or buprenorphine/samidorphan combinations, concerns do persist about the use of such treatments with selected, more vulnerable patient groups. For example, the results of a small study of depressed patients who had responded to intravenous ketamine infusions found that pretreatment administration of the opiate antagonist naltrexone could attenuate or even block the desired antidepressant effects of this closely related treatment.[4] When reviewing potential patients for adjunctive therapy with intranasal esketamine, one must keep in mind that it is a Schedule III controlled substance and that patients with more extensive substance abuse histories were not included in the Phase III studies of this medication.

I suspect that Dr. Skaff would agree with me that we need to be humble about all that we do not know about how our drugs actually work. In the midst of the current cycle of enthusiasm for novel targets for drug development, it is sobering that rapastinel, a drug with such a promising rationale based on a wealth of preclinical data,[5] could fail so badly in Phase 3 clinical trials. Is it relevant that, unlike ketamine, rapastinel has minimal euphorigenic or dissociative effects?

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Perhaps it will be eventually shown that rapastinel at a different dose or delivered in a different way also has meaningful antidepressant effects. Or perhaps our definition of TRD is too coarse to identify a subset of patients who do benefit from rapastinel. In any event, as imperfect as the current criteria for TRD may be, they have provided a starting point for research on the next generation of medications and, for the first time in several decades, our patients with the most difficult-to-treat depressive illnesses have truly novel options available.

Sincerely,
Michael E. Thase, MD.

Disclosures. Michael E. Thase, MD, is a professor in the Department of Psychiatry and Director of the Mood and Anxiety Disorders Treatment and Research Program of the Perelman School of Medicine at the University of Pennsylvania and the Corporal Michael J Crescenz VAMC in Philadelphia, PA. Dr. Thase receives research support from the Agency for Healthcare Research and Quality, Alkermes, AssureRx, Avanir, Forest, Intracellular, Janssen, Lilly, National Institutes of Health, Otsuka, and Takeda, and is a consultant/advisor to Alkermes, Allergan, AstraZeneca, Bristol-Myers Squibb, Cerecor, Fabre-Kramer, Forest, Gerson Lehman, GlaxoSmithKline, Guidepoint Global, H. Lundbeck, Lilly, MedAvante, Merck, Moksha8, Neuronetics, Ortho-McNeil, Otsuka, Pamlab (Nestle), Pfizer, Roche, Shire, Sunovion, Takeda, and Trius. Dr. Thase receives royalties from the American Psychiatric Foundation, Guilford Publications, Herald House, MedAvante, and W.W. Norton & Company. Dr. Thase's spouse is employed by Peloton Advantage, which does business with several pharmaceutical companies.

References

1. Rothschild AJ, Dunlop BW, Dunner DL, Friedman ES, Gelenberg A, Holland P, *et al*. Assessing rates and predictors of tachyphylaxis during the prevention of recurrent episodes of depression with venlafaxine ER for two years (PREVENT) study. *Psychopharmacol Bull*. 2009;**42**(3):5–20.
2. Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, *et al*. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry*. 2019. doi:10.1001/jamapsychiatry.2019.1189. (Epub ahead of print)
3. Thase ME, Stanford AD, Memisoglu A, Martin W, Claxton A, Bodkin JA, *et al*. Results from a long-term open-label extension study of adjunctive buprenorphine/samidorphan combination in patients with major depressive disorder. *Neuropsychopharmacology*. 2019. doi:10.1038/s41386-019-0451-3. (Epub ahead of print)
4. Williams NR, Heifets BD, Blasey C, Sudheimer K, Pannu J, Pankow H, *et al*. Attenuation of antidepressant effects of ketamine by opioid receptor antagonism. *Am J Psychiatry*. 2018;**175**(12):1205–1215.
5. Moskal JR, Burgdorf JS, Stanton PK, Kroes RA, Disterhoft JF, Burch RM, *et al*. The development of rapastinel (formerly GLYX-13): a rapid acting and long lasting antidepressant. *Curr Neuropharmacol*. 2017;**15**(1):47–56.

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