

Letter to the Editor

Cite this article: Skaff R (2021). Tachyphylaxis and desensitization depression. *CNS Spectrums* 26(3), 191–192.
<https://doi.org/10.1017/S1092852919001445>

Received: 11 August 2019

Accepted: 12 August 2019

Key words:

Tachyphylaxis; depression; desensitization.

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Dear Editor,

Depression is a heterogeneous disorder that can assume many forms and is often difficult to treat successfully. The true etiology of depression remains unknown. However, the hypotheses are numerous as they range from psychological to genetic and from psychosocial to medical. Unfortunately, depression treatments don't always work and one-third of patients who began treatment remained depressed despite having up to 4 sequential treatment trials.¹

The article in the December 2017 issue of *CNS Spectrums* titled “New medications for treatment-resistant depression: a brief review of recent developments,” discussed the latest psychotropic treatments that might target in the future treatment-resistant depression (TRD). The author takes the reader on a panoramic view of what new drugs for depression might look like, such as the dissociative anesthetic ketamine, and other related therapies like Rapastinel that is thought to be a partial agonist of an allosteric glycine site of the NMDA receptor. The author also covered other drugs such as Lamicemine as a low tapping NMDA channel blocker, as well as drugs that target the opiate system and the immune system, which are all brewing in the pipelines to be tried for TRD.¹ Unfortunately, the author did not address the reason why old drugs such as SSRIs, SNRIs, SARIs, DRIs, TCAs, and MAOIs have failed over one-third of the depressed patients due to antidepressant treatment (ADT) tachyphylaxis, and eventually rendering the condition into a TRD. Therefore, we should wonder whether these new elixirs that the author discussed will eventually have the same destiny as their predecessors. Interestingly, a new and large research that was published in the *British Medical Journal* indicated that most new drugs entering the market, particularly medications for neurologic and psychiatric disorders provide no additional benefit over and above the existing standard of care.²

The Center for Medicare and Medicaid (CMS) defines TRD as a “failure of treatment to produce response or remission for patients after two or more treatment attempts of adequate dose and duration, but no clear agreement exists about this definition.”³ Experts also suggest that before treating TRD, however, due diligence is recommended as several conditions are possible causes of relative or “pseudo” TRD.⁴

However, to understand TRD we must discuss ADT tachyphylaxis and tolerance. What is ADT tachyphylaxis, and does it intertwine with treatment-resistant depression? Furthermore, are the current definitions of resistance and tolerance inadequate, thus creating an opaque impression leading to ineffective treatments?

ADT tachyphylaxis is generally defined as a rapidly decreasing response to a drug or physiologically active agent after administration of a few doses. “Tachy” in Greek means swift, and “phylaxis” means guarding, protection; the term “antidepressant tachyphylaxis” was termed by Leib and Balter in 1984.⁵ In addition, antidepressant tachyphylaxis is also known as antidepressant tolerance, antidepressant “poop out” which illustrates a condition in which a depressed patient loses a previously effective antidepressant treatment response despite staying on the same drug and dosage for maintenance treatment. It has also been suggested that antidepressant tachyphylaxis is a form of relapse related to evolving drug tolerance.⁶ Although the real frequency of the tachyphylaxis phenomenon is unclear, it may be as high as 33% during the pharmacological treatment of depression.⁶ Additionally, experts tend to assume that a loss of response such as in ADT tachyphylaxis is distinct from a non-response to treatment (resistance) or a partial (inadequate) ADT response. So, what causes this drug tolerance? Generally, tolerance leads to increasing doses of a drug being required to produce the same effect. A presumed mechanism responsible for tolerance is accelerated metabolism, for example, by induction of hepatic enzymes such as the cytochrome P-450 system enzymes. Other possible mechanisms could be the result of a decrease in binding affinity between a drug and receptor and a decrease in the number of receptor (downregulation).⁷

Interestingly, despite the surmised explanations above, the mechanisms responsible for drug tolerance or resistance are not always known. Thus, it becomes necessary to ask the following questions:

- Is it possible that the presumed mechanisms of action of the existing psychotropic drugs may not be as accurate as the manufacturers have claimed? Or could the initial response to ADT is nothing more than a placebo effect that fades away over time?

- Is it feasible that brain receptors would follow the same pattern that tolerant to resistant bacteria develop after being bombarded with a bacteriocidal drug?
- Does the trellis of receptor networks experience a conformational change leading to genetic mutation induced by ADT repeated exposure?

The understanding of these mechanisms has significant implications not only in psychiatric treatment but in every medical treatment.

Due to the uncertainty surrounding the definitions and causes of tolerance and resistance, I am suggesting that we should consider ADT tolerance as a state of gradual receptor desensitization leading to total receptor deafness triggered by the protracted barrage of neurochemicals over targeted receptors; thus a conformational change in these receptors might occur engendering the purported tolerance mechanisms listed above leading to some sort of genetic mutation. This proposed conformational change might be a self-preservation mechanism (just like in bacteria) aimed at safeguarding the homeostasis and integrity of the receptors' own terrain, thus inducing a "withdrawn and deaf-like" state to tune out the bombardment noise caused by antidepressants.

Finally, we should consider that tolerance and resistance are interweaved, and a new and clear definitions must be established to reduce clinical ambiguity for practitioners. I am also proposing that "treatment-resistant depression" is renamed as "desensitization depression (DD)" or "hyposensitivity depression (HD)" in weak

responders. In addition, research should be more geared toward the study of the placebo effect, as well as the development of evidenced-based effective titration strategies that will reverse and/or deter the desensitization process, instead of the ongoing "new drug approach" that tags the same receptors or assails new ones with the same end results.

Disclosure. Richard Skaff has nothing to disclose.

References

1. Thase E. New Medications for treatment-resistant depression: a brief review of recent developments. *CNS Spectr*. 2017;**22**: 42–47.
2. Wieseler B, McGauran N, Kaiser T. New drugs: where did we go wrong and what can we do better? *BMJ* 2019;**366**: 14340.
3. Gaynes BN, Asher G, Gartlehner G, *et al*. Definition of Treatment Resistant Depression in the Medicare Population. <https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id105TA.pdf>. Published February 9, 2018.
4. Serretti A, Fabbri C. Factors that predispose patients to treatment resistant depression. *Psychiatr Times*. 2014;**31**(9): 1–2.
5. Katz G. Tachyphylaxis/tolerance to antidepressant medications. A review. *Isr J Psychiatry Relat Sci*. 2011;**48**(2): 129–135.
6. Targum S. (2014) Identification and treatment of antidepressant tachyphylaxis. *Innov Clin Neurosci*. 2014;**11**(3–4): 24–28.
7. Lynch S. Tolerance and Resistance. <https://www.merckmanuals.com/professional/clinical...drugs/tolerance-and-resistance>. Published November 2016.