
LETTER TO THE EDITOR

Does Rapid Tryptophan Depletion Induce Depressive Relapse?☆

Moore et al offer an excellent, comprehensive scientific review of tryptophan depletion experiments (Moore et al. 2000). A key issue examined in the article is the "reported ability [of rapid tryptophan depletion] to induce depressive relapse in euthymic patients." The appropriateness of defining transient depressive symptom exacerbation as a "depressive relapse" is a matter of scientific, clinical, and ethical significance. The description of tryptophan depletion as provoking "relapse" in euthymic patients misleadingly suggests that these experiments make patients clinically depressed for the sake of scientific investigation, thus provoking unwarranted ethical criticism.

The authors note that "depressive relapse" has been defined variously by different investigators, and they endorse the "most restrictive" definition adopted by Delgado and his colleagues: "an increase in pre-challenge HDRS by at least 50% and >17." The authors do not provide systematic data on the duration of provoked symptom worsening. Delgado et al. described tryptophan depletion in 46 patients in remission following antidepressant treatment, of whom 24 experienced "depressive relapse." (Delgado et al. 1991) They observed that "All of these patients returned to their clinically remitted state within 24 to 48 hours after the TRP-depleting amino acid drink."

We contend that such transient symptom exacerbation does not amount to depressive relapse. Depressive relapse constitutes a serious and persisting emergence of symptoms that warrants pharmacological intervention. (Frank et al. 1991) Symptom exacerbation lasting

from a few hours to up to two days is clinically and ethically significant in view of the distress that it may cause. (Miller and Rosenstein 1997) But these results do not support a claim that tryptophan depletion experiments induce clinically significant relapse in some patient volunteers. The definition of "depressive relapse" employed in the tryptophan depletion and other challenge paradigms is problematic because it focuses solely on symptom severity and not on duration. More careful characterization of symptom provocation associated with psychiatric challenge studies promotes both scientific and ethical accuracy.

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REFERENCES

- Moore P, Landolt H-P, Seifritz E, Clark C, Bhatti T, Kelsoe J, Rapaport M, Gillin JC (2000): Clinical and physiological consequences of rapid tryptophan depletion. *Neuropsychopharmacology* 23:601-622
- Delgado PL, Price LH, Miller HL, Salomon RM, Licinio J, Krystal JH, Heninger GR, Charney DS (1991): Rapid serotonin depletion as a provocative challenge test for patients with major depression: relevance to antidepressant action and the neurobiology of depression. *Psychopharmacology Bulletin* 27:321-330
- Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MW (1991): Conceptualization and rationale for consensus definitions of terms in major depressive disorder. *Archives of General Psychiatry* 48:851-855
- Miller FG, Rosenstein DL (1997): Psychiatric symptom-provoking studies: an ethical appraisal. *Biological Psychiatry* 42:403-409

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