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LETTER TO THE EDITOR

Response☆

We heartily concur with Miller and Rosenstein that the operational definition of "depressive relapse" in the context of psychiatric challenge studies is in need of discussion and refinement, from a clinical, scientific and ethical standpoint. We agree that the issue of symptom duration tends to be overlooked in challenge paradigms, and that there may be too much reliance on the use of cutoff scores of symptom severity to determine "depressive relapse." Their suggestion that the definition be augmented with an awareness of symptom duration is important.

To our knowledge, reports of severe exacerbation of depressive symptoms are relatively uncommon following rapid tryptophan depletion challenges. Details regarding the duration of symptom worsening are limited, but in general it appears to be comparatively briefly (say, 6–48 hours), and symptoms reverse and/or normalize without intervention, along a timecourse similar to repletion of tryptophan in plasma. Clearly, from a scientific and ethical perspective, subjects need to be evaluated systematically for a long enough period of time to know the duration and severity of the effects of the challenge. But how long is long enough? And how long should we expect the clinical effect to last given the relatively brief duration of the physiological challenge? Certainly, more discussion is warranted about the definition of "depressive relapse." While duration of symptoms is important, we believe severity of symptoms is even more important. We would define even a brief hours-long period of suicidal ideation as a true "depressive relapse." Fortunately, this has never happened in our experience, and if it did, we would probably discontinue these experiments as unethical.

From our own experience we note subtle symptom changes may persist following rapid tryptophan depletion for longer periods of time than investigators may have been led to expect. Patients may require thorough follow-up for an appropriate period of time.

We reiterate our belief that rapid sharing of serious adverse events should be an ethical requirement among investigators using these paradigms. Investigators working independently in different locations need a mechanism to be aware of uncommon but serious side effects associated with challenge paradigms. Toward that end, that there may be a need to develop a central oversight committee or reporting center such as those used in multi-site clinical trials.

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