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To the Editor:

Acute tryptophan depletion (ATD) induces depressive symptoms in subgroups of recovered depressed patients, including those with seasonal affective disorder (SAD) (Van der Does, 2001*a*, review). The mood-lowering effect of ATD has been demonstrated in SAD patients after treatment with light therapy (Lam *et al.* 1996; Neumeister *et al.* 1997), as well as during natural summer remission (Neumeister *et al.* 1998). However, Lam *et al.* (2000) found no significant differences between response to ATD and response to sham depletion in medication-free patients with SAD during summer remission. The authors conclude that summer remission is not dependent on plasma tryptophan (Trp) levels in the same manner as that of remission after light therapy. Consequently, this study is now being cited as a failure to replicate (Bell *et al.* 2001; Neumeister *et al.* 2001). Lam *et al.* suggest that differences in study samples, e.g. different duration of remission or level of residual symptoms may account for the differences between their study and others. However, in a recent reanalysis of six pooled ATD studies (Booij *et al.* 2002), neither duration of remission nor residual symptoms were not found to predict response to ATD, making this explanation less likely.

A closer look at the findings by Lam *et al.* (2000) reveals that their conclusion – that summer remission is not dependent on plasma Trp levels – is unwarranted. Six of 12 patients in the study had a clinically significant response to ATD, but three patients responded to sham depletion. It is not reported whether the patients who responded to sham depletion, also responded to ATD. Considering the small sample size, the 50% response rate to ATD is not very different from the 72·7% (8/11) reported by Neumeister *et al.* (1998). However, in the latter study no one responded to sham depletion. The study by Lam *et al.* (2000) is unique in the fact that so many patients responded to sham depletion. Response to sham Trp depletion is so rare that it has even been suggested to abandon placebo testing in previously researched populations (Van der Does, 2001*a*). It is important to note, however, that not all sham procedures are inactive and equivalent to placebo. Lam *et al.* (2000, p. 84) acknowledge the possibility that sham depletion may in fact result in slight brain serotonin depletion, even if serum Trp levels increase (in their study, the increase of total Trp was 113%). This is because the levels of other amino acids also increase, and Trp competes with large neutral amino acids (LNAAs) for the same transport system into brain. However, the resulting brain serotonin depletion may be more than slight: Weltzin *et al.* (1994), using the same sham depletion procedure, found a substantial (well above 100%) rise of plasma Trp, yet a 55% decrease of the plasma Trp/LNAA ratio. Trp/LNAA ratios were not reported by Lam *et al.* (2000). It has been suggested that there may be a threshold rather than a linear relationship between levels of Trp and mood response following ATD (Spillmann *et al.* 2001; Van der Does, 2001*b*). It seems very well possible that the three responders to sham depletion in the Lam *et al.* (2000) study had reductions of plasma Trp/LNAA ratios well above the hypothesized threshold.

In summary, Lam *et al.* (2000) found a 50% response rate to ATD in a sample of 12 SAD patients during summer remission. Although this response rate is within the typically reported range (Van der Does, 2001*a*), the authors also observed that this rate was not significantly different from control testing, and concluded that SAD summer remission is not dependent upon plasma Trp. The authors focus their discussion on the question of why their results are different from Neumeister *et al.* (1998), but fail to appreciate fully that their control findings are anomalous, and not their ATD findings. The increase in Hamilton ratings after both the depletion and control testings was attributed to the aversive physical side effects of the amino acid drinks rather than to specific mood effects.

If that were true, response to placebo testing would be quite common in ATD studies. As noted above, it is in fact virtually absent.

If still possible, the findings reported by Lam *et al*. (2000) should be supplemented with the Trp/LNAA ratios before and after sham testing. This may determine whether the control findings are really anomalous, or whether the three responders had in fact plasma Trp/LNAA reductions at which a mood response could be expected. It would also be important to know whether the three responders to 'control testing' had also responded during the ATD session. The reason is that little is known about the test–retest reliability of ATD. In a study with healthy subjects, poor temporal stability of ATD effects has been observed (Ellenbogen *et al*. 1996). However, the effects of ATD in healthy subjects are quite small to begin with, so more data on this in clinical samples would be valuable.

In conclusion, the most significant finding by Lam *et al*. (2000) concerns their control procedure. Their ATD findings are in fact quite normal, and do not justify their conclusion that SAD summer remission is not dependent on plasma Trp levels. Finally, this study underscores the necessity of measuring competing LNAAs in studies in which the level of plasma Trp is manipulated.

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