Low-Dose Tryptophan Depletion

To the Editor:

Acute tryptophan depletion (ATD) is a popular method to investigate the effects of lowered serotonin function in humans. Acute tryptophan depletion induces a temporary depressive 'relapse' in 50–60% of remitted depressed patients treated with serotonergic antidepressants. In healthy individuals, ATD has no or minor mood effects, but cognitive effects have been found in both healthy and recovered depressed individuals (Booij et al 2003).

The magnitude of the reduction of plasma tryptophan concentrations following ATD depends on the amount and composition of the amino acid mixture (Young et al 1989) and whether a pre-test low tryptophan diet is included. It has been suggested that a threshold exists that needs to be exceeded before any behavioral effects occur, since studies in which the plasma tryptophan reduction was lower than 70% generally do not find any symptomatic effects (van der Does 2001b). However, depression-congruent effects on sleep architecture have been observed at moderate tryptophan reductions (Bhatti et al 1998). The placebo procedure developed by Krahn et al (1996) may be suitable as a low-dose ATD procedure (van der Does 2001a). Since this procedure reduces plasma tryptophan concentrations by 40–50%, and has been found not to affect mood (Booij et al 2005), it allows for the investigation of possible dose-response effects.

Booij et al (2005), using the Krahn et al (1996) method as low-dose ATD, found that ATD had a dose-dependent effect on selective attention (Stroop color-word interference) in remitted depressed patients, but no other cognitive effects of low-dose ATD were observed. Merens et al (unpublished data) observed no effects of low-dose ATD on attention, memory, and accuracy of emotion recognition in remitted depressed patients. Two recent papers have reported much stronger effects of low-dose ATD. Hayward et al (2005) found that low-dose ATD had no effects on mood ratings in unmedicated recovered depressed subjects, but that it increased the emotion-potentiated startle reflex, impaired recognition of happy faces and initial recall memory and increased emotional Stroop interference. Some cognitive effects were also observed in healthy controls. Munafò et al (2006) reported that low-dose ATD slightly increased self-rated depressive symptoms in medicated recovered depressed patients and also increased Stroop interference for social threat words.

The low-dose mixture used by Hayward et al (2005) and Munafò et al (2006) consisted of eight amino-acids (31.2 g), whereas the Krahn et al (1996) procedure consists of 15 amino-acids (25.7 g). We calculated the plasma tryptophan reductions obtained by Hayward et al (2005), and found that low-dose ATD decreased plasma tryptophan levels by 73.9% in recovered depressed patients. The tryptophan/large neutral amino acids (LNAA) ratio decreased by 86.9%. This suggests that Hayward et al (2005) studied high-dose ATD rather than low-dose. The reductions cannot be calculated from the report by Munafò et al (2006), but this study used the same procedure and partly the same sample. Viewing these studies as high-dose ATD studies resolves the inconsistencies with the studies by Booij et al (2005) and Merens et al (unpublished data). It also explains the symptomatic effects in the Munafò et al study. However, high-dose ATD would be expected to have increased symptoms in Hayward et al's paper. This may be explained by the fact that patients in this study had a relatively low number of previous episodes, which predicts a weaker response to ATD (Booij et al 2002).

There is no generally accepted definition of high-dose or low-dose ATD. Hayward et al (2005) presented their study as a low-dose ATD study on the basis of the amount of amino acids used. However, peripheral biochemical measures indicate that this study may be considered a high-dose ATD study. In our view, the term low-dose should reflect the decrease of plasma tryptophan concentrations and not the amount and content of the ATD mixture. Future research should carefully consider which terminology is used to prevent misinterpretation and biochemical data should be reported in detail.

Wendelien Merens
Willem van der Does

Department of Psychology
Leiden University
Wassenaarseweg 52
2333 AK Leiden, The Netherlands

Bhatti T, Moore P, Stahl S, Clark C, Gillin JC, Seifritz E, et al (1998): Effects of a tryptophan-free amino acid drink challenge on normal human sleep electroencephalogram and mood. *Biol Psychiatry* 43:52–59.

Booij L, van der Does AJW, Benkelfat C, Bremner J, Cowen PJ, Fava M, et al (2002): Predictors of mood response to acute tryptophan depletion: A reanalysis. *Neuropsychopharmacology* 27:852–861.

Booij L, van der Does AJW, Haffmans PMJ, Riedel WJ, Fekkes D, Blom MJB (2005): The effects of high-dose and low-dose tryptophan depletion on mood and cognitive functions of remitted depressed patients. *J Psychopharmacol* 19:267–275.

Booij L, van der Does AJW, Riedel WJ (2003): Monoamine depletion in psychiatric and healthy populations: Review. *Molecular Psychiatry* 8:951–973.

Hayward G, Goodwin G, Cowen P, Harmer C (2005): Low-dose tryptophan depletion in recovered depressed patients induces changes in cognitive processing without depressive symptoms. *Biol Psychiatry* 57:517–524.

Krahn L, Lu P, Klee G, Delgado P, Lin S, Zimmermann R (1996): Examining serotonin function: A modified technique for rapid tryptophan depletion. *Neuropsychopharmacology* 15:325–328.

Munafò MR, Harmer C, Hayward G (2006): Selective processing of social threat cues following acute tryptophan depletion. *J Psychopharmacol* 20:33–39.

van der Does AJW (2001a): The effects of tryptophan depletion on mood and psychiatric symptoms. *Journal of Affective Disorders* 64:107–119.

van der Does AJW (2001b): The mood-lowering effect of tryptophan depletion: Possible explanation for discrepant findings. *Arch Gen Psychiatry* 58:200–201.

Young SN, Ervin FR, Pihl RO, Finn P (1989): Biochemical aspects of tryptophan depletion in primates. *Psychopharmacology (Berl)* 98:508–511.

doi:10.1016/j.biopsych.2006.09.024