Psychological Medicine, 2003, **33**, 1133–1137.
Printed in the United Kingdom

CORRESPONDENCE

Psychological Medicine, **33**, (2003).
DOI: 10.1017/S0033291703218523

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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The Author's reply:

We appreciate Dr Van der Does' comments and close reading of our study. In any negative study, particularly one that conflicts with other data (Neumeister *et al.* 1998), it is important to examine potential reasons for the results. He focuses on the fact that 3/10 patients showed depressive relapse on the Hamilton Depression Rating Scale (HAM-D) during the control depletion session, compared to 5/10 during the active depletion session, and wonders whether this was due to a relative reduction in the tryptophan/LNAA ration. In fact, as noted by Dr Van der Does, in our discussion we specifically mentioned that alterations in the tryptophan/LNAA ratio during the control session might have complicated the results (Lam *et al.* 2000). Unfortunately, we were not able to examine the tryptophan/LNAA ratio in this study, but we agree that future studies should incorporate this important measure.

However, other possibilities must also be entertained. We suggested that factors such as length of remission and suicidality might be different between studies. At the time of publication we did not have access to the pooled analysis of Booji *et al.* (2002) showing that length of remission was not related to depressive relapse.

However, the pooled analysis also found that some clinical factors, such as chronicity and suicidality, were indeed associated with response to tryptophan depletion. Hence, differences in these and other clinical factors may still explain discrepant results between studies.

Although Dr Van der Does dismisses the possibility that the high scores on the HAM-D were related to physical symptoms of discomfort with the amino acid drink instead of a true depressive relapse, we felt that this was a potentially important possibility. Other behavioural measures evaluated in this sample indicate that a significant depressive relapse did not occur in the patients. For example, we reported in the paper that the scores on the Profile of Mood States, a sensitive measure of mood change, were low during both depletion and control sessions, indicating that a core mood component of relapse was not seen. Although not reported in our paper, there was a similar result with the Depressed Mood item of the HAM-D, again suggesting that a true depressive relapse was not seen during the tryptophan depletion session. Finally, to assess a qualitative measure of relapse, we asked patients how similar was their mood state after depletion/control sessions to their usual winter depressive state. Most patients in this study did not identify their mood state as depressed following depletion/control sessions. This contrasts with our previous results in tryptophan depletion in patients with seasonal affective disorder after short-term remission from light treatment (Lam *et al.* 1996), and also after catecholamine depletion in summer remission (Lam *et al.* 2001). In the latter study, the depressive relapse was much more robust and consistent (9/9 relapses during catecholamine depletion *versus* 2/9 during the control session) and the symptoms experienced were qualitatively very similar to the patients' winter depressive episodes.

In summary, we believe that our data show that there is no significant mood change with tryptophan depletion in patients with SAD in summer remission, despite the changes in HAM-D scores found in some patients and control subjects. Given the potential confounding factors and the typically small sample sizes of monoamine depletion studies, it seems clear that a control depletion condition is still warranted to provide internal validation for these studies.

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Psychological Medicine, **33**, (2003).
DOI: 10.1017/S003329170322852X

To the Editor:

We would like to give credit to Jan Scott and Tom Sensky for their accurate and insightful overview of the methodological considerations for conducting psychotherapy trials in primary care (Scott & Sensky, 2003).

However, we feel the authors have overstated the importance of effectiveness research (does it work in routine care?) in contrast to efficacy research (does it work under ideal circumstances?). We disagree with the notion that 'efficacy studies are not necessarily helpful in deciding whether an intervention would work in day-to-day practice' (Scott & Sensky, 2003). In our opinion, efficacy studies should be first choice at all times, especially when the research field is as underdeveloped as psychotherapy research.

An efficacy trial needs a high degree of internal validity in order to produce interpretable findings. A prerequisite is comparability of populations, intervention circumstances and effect measurements. If not, a published trial quite often has a false positive result (Knipschild,

2002). In that sense, an effectiveness study with a higher likelihood of bias may produce less reliable findings. Consequently, the first challenge for psychotherapy research lies in finding efficacious treatments.

Scott & Sensky argue that attrition (treatment dropout) is less of an issue in efficacy studies since these are not conducted in real clinical settings. However, treatment dropout is as much an indication of treatment acceptability in efficacy studies as it is in effectiveness studies. Also, efficacy studies can be especially helpful when an intervention is found to be ineffective: if the intervention does not work under ideal circumstances, it is very unlikely the intervention will be of value in routine care.

Is it unnecessary then to evaluate the use of psychotherapy in routine care? Most definitely not. We merely claim that one does not need effectiveness studies to do so. After interpretation of the findings of available efficacy studies, therapists should mainly use their clinical judgement to decide whether a certain treatment is useful for certain patients.

In general, we argue that there is no first need for more effectiveness studies of psychotherapy in primary care. A greater problem is that there are too few efficacy studies.

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The Authors reply:

We agree with Huibers and Knipschild that well-designed efficacy studies can have high internal validity – with their results measuring what was intended, with minimisation of bias and confounding. By contrast, pragmatic, effectiveness studies emphasize external validity – the generalizability of the study results to other similar real-life settings and patient samples.

There is often a trade-off between external and internal validity. For example, consider a randomized controlled trial in which cognitive therapy is compared with general practitioner contact for mild depression in primary care. Assume that the sample comprises only those with an ICD-10 diagnosis of a mild or moderate depressive episode, and excludes patients who are suicidal, or have a Beck Depression Inventory score >29. Assume that all patients receive six sessions of therapy that strictly follows a manual, and that patients who fail to attend at least four therapy or control sessions are also excluded from the study. Such a study design is typical of an efficacy study. The more homogeneous the sample and the intervention, the more likely that statistically significant differences will be found between the experimental and comparison interventions. We agree with Huibers & Knipschild that if a valid efficacy study fails to show benefits for the experimental intervention, then there is no point in testing the same intervention in an effectiveness study. However, we disagree that clinicians can use their clinical judgement to extrapolate from such a study to 'real-world settings'. How could a clinician judge the likelihood of symptomatic improvement from this intervention for patients who are suicidal, specifically excluded from the study? How, other than by conducting a pragmatic randomized controlled trial, will clinicians know what proportion of their own patients would remain engaged for at least four therapy sessions? If the therapeutic benefits in this 'ideal' study are modest, how can one quantify the effect of doing the same intervention in the real clinical world? It is for this reason that standard guidelines for critical appraisal of intervention studies have made a clear distinction between the (internal) validity of a study (Guyatt *et al.* 1993), and its clinical importance – or external validity (Guyatt *et al.* 1994; Dans *et al.* 1998).

As noted in our editorial, criticisms that randomized controlled trials are irrelevant in psychotherapy (Seligman, 1995; Persons & Silberschatz, 1998) have focused on efficacy studies. It has been argued that in clinical practice, psychotherapists do not confine their interventions to those with a specific DSM or ICD diagnosis, that they offer a flexible number of therapy sessions according to the individual

patient's needs, and that they do not slavishly follow a treatment manual but adapt their therapy to the individual patient. Although each of these factors would enhance the internal validity of a research study, we agree with the critics that these factors also inevitably compromise external validity. Some evidence has been presented that for cognitive therapy for depression, results of interventions in clinical practice are comparable with those from efficacy studies (Persons *et al*. 1999). However, this is unlikely to be a general finding, for all conditions and across a variety of different forms of psychological intervention. We therefore remain convinced that application of psychotherapy research in real clinical settings depends on good pragmatic randomized controlled trials.

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