# Correspondence

EDITED BY STANLEY ZAMMIT

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## Smaller trials for better evidence

The interesting debate between Parker and Anderson & Haddad (2003) suggests more fundamental reasons to question prevailing research paradigms and designs in respect of the efficacy of and indications for psychotropic medicines. That the clinical trial industry reveals even marginal drug effects may be seen as surprising given the virtual absence of any basis for a taxonomy of mental disorders, other than the syndromal classifications used in psychiatric practice. There is little evidence that the major syndromes align with any readily defined pathophysiological variance. Group heterogeneity in trial work, as the debaters remark, will therefore attenuate the evidence for substantial drug treatment effects, sometimes to vanishing point. Meta-analysis of such data may not be much more revealing, compounding the influence of variable sampling in individual trials and publication bias.

These side-effects of the randomised controlled trial ethos are not greatly mitigated in the field of organic mental disorders. At huge expense, multicentre trials of cholinesterase inhibitors in patients classified as probably having Alzheimer's disease have shown only very modest (and to many observers still unconvincing) effects on cognitive and neuropsychiatric outcomes (e.g. Lanctôt *et al*, 2003). This is because these conditions, pace distinguished efforts at nosological definition in life, are also heterogeneous. This variability, already evident from detailed clinical and neuropsychological assessment, is further revealed by functional and structural analysis of the brain. It is these data which might best inform sampling for therapeutic trials. Studies on a smaller scale, therefore, targeting the more readily defined Lewy body dementia (e.g. McKeith *et al*, 2000) or more intensively characterised and monitored patients with Alzheimer's disease (e.g. Venneri *et al*, 2001) in both double-blind and open-label designs, can convincingly demonstrate the nature and the modalities of efficacy using cholinesterase inhibitors. In the same way, studies of smaller groups of patients receiving treatment for depression may reveal correlations between clinical features and treatment responses that are more likely to guide the selection of therapy for individual patients (Mayberg, 2003).

Large randomised controlled trials, by submerging variation in the interest of marginal statistical significance, seem to offer limited hope of significantly improving the evidence that guides clinical practice. Studies of cognitive and pharmacological interventions might best be carried out with smaller patient groups for whom there has been detailed assessment of relevant pathophysiological and cognitive variance, as well as the manifest clinical symptoms.

### *Declaration of interest*

M.F.S. and A.V. have received honoraria and support for attending scientific meetings, been members of advisory boards and received research grants from companies involved in the manufacture and marketing of cholinesterase inhibitors.

**Lanctôt, K. L., Herrman, N., Yau, K. K., *et al* (2003)** Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. *Journal of the Canadian Medical Association*, **169**, 557–564.

**MacKeith, I. G., Del Ser, T., Spano, P. F., *et al* (2000)** Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet*, **356**, 2031–2036.

**Mayberg, H. S. (2003)** Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimized treatment. *British Medical Bulletin*, **65**, 193–207.

**Parker, G./Anderson, I. M. & Haddad, P. (2003)** Clinical trials of antidepressant medications are producing meaningless results (debate). *British Journal of Psychiatry*, **183**, 102–104.

**Venneri, A., Shanks, M. F., Staff, R. T., *et al* (2001)** Cerebral blood flow and cognitive responses to rivastigmine treatment in Alzheimer's disease. *NeuroReport*, **13**, 83–87.

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## Pendulum management in secure services

Tilt (2003) defends himself clearly against the criticisms of Drs Exworthy & Gunn (2003). However, he does not emphasise the extent to which they have misrepresented aspects of the Tilt Report (Tilt *et al*, 2000). Specifically, Exworthy & Gunn state, following their quote from the Report concerning the relationship between security and therapy, 'one should go further because in high secure hospitals therapy in its widest sense is an integral part of security'. This virtually paraphrases the Report itself: 'Security is the responsibility of all personnel in a high security hospital and . . . good security facilitates good therapy and vice versa' (paragraph 8.2).

There also appears to be a marked absence from this debate of both historical and organisational perspectives. Rapoport (1960) suggested, in considering the institutional dynamics of therapeutic institutions, that 'disturbances were partly a function of cycles of abdication of authority, in the name of permissiveness, followed by authoritarianism to restore order'. The consequences of the report on the Ashworth Hospital inquiry (Blom-Cooper *et al*, 1992) (Ashworth at that time being an abusive, authoritarian institution) were clearly thought by Fallon *et al* (1999) to relate to a breakdown of security (permissiveness), leading to the Tilt Report (which has been perceived by many in secure services as authoritarian).

Perhaps attempting to understand this cycle more, and how it may relate to the complex (and potentially contradictory) tasks facing secure psychiatric services, might reduce the likelihood of yet more scandals, inquiries and reports in the future. Scott (1975) suggested that 'detaining custodial institutions have two aims, one therapeutic, the other custodial. These can and should be complementary, but there is a tendency for these functions to polarise out and eventually split like a living cell into two separate institutions'. The debate between Exworthy & Gunn and Tilt illustrates the recurring nature of this phenomenon.



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Perhaps this debate needs to move on to a creative engagement with this process.

**Blom-Cooper, L., Brown, M., Dolan, R., *et al* (1992)** *Report of a Committee of Inquiry into Complaints about Ashworth Hospital*. London: HMSO.

**Exworthy, T. & Gunn, J. (2003)** Taking another tilt at high secure hospitals. The Tilt Report and its consequences for secure psychiatric services. *British Journal of Psychiatry*, **182**, 469–471.

**Fallon, P., Bluglass, R., Edwards, B., *et al* (1999)** *Report of the Committee of Inquiry into the Personality Disorder Unit, Ashworth Special Hospital*. London: Stationery Office.

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**Scott, P. D. (1975)** *Has Psychiatry Failed in the Treatment of Offenders?* (The Fifth Denis Carroll Memorial Lecture). London: Institute for the Study and Treatment of Delinquency.

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## Sertraline and exposure therapy in social phobia

I read with interest the article by Haug *et al* (2003), but was puzzled by the conclusion they drew from their data.

After a 24-week study comparing sertraline, sertraline plus exposure, exposure plus placebo, and placebo in patients with social anxiety disorder (Blomhoff *et al*, 2001), patients were followed up at week 52. In the summary the authors conclude that 'Exposure therapy alone yielded a further improvement during follow-up, whereas exposure therapy combined with sertraline and sertraline alone showed a tendency towards deterioration after the completion of treatment'. This seems to be a misleading interpretation of their data.

Haug and colleagues did not mention the primary efficacy measures of their study in their paper. Reading the original paper by Blomhoff *et al*, I find that the primary efficacy measures were numbers of responders or partial responders on the Clinical Global Impression – Social Phobia (CGI–SP) and the Social Phobia Scale (SPS). In the first study, treatment with sertraline was superior to placebo, but exposure was not. For example, 45.5% of the patients treated with sertraline plus exposure were responders compared with 33.0% of the patients treated with exposure plus placebo. I wonder why it was not mentioned in the second paper whether the three active groups differed from placebo and from each other on the primary efficacy measures.

Instead, Haug *et al* report only relative changes of mean scores without adjusting for the large absolute differences at termination of the acute study (week 24). After 52 weeks, exposure patients only caught up to the already better scores of the sertraline groups. From both papers, I calculated the following total mean changes for weeks 0–52 by adding the mean changes for weeks 0 to 24 and the ones for weeks 24 to 52 and found: 1.68 for placebo, 2.02 for sertraline plus exposure, 1.92 for sertraline, and 1.88 for exposure plus placebo on the CGI–SP overall severity. For the SPS, I found the following mean changes: 12.09 for placebo, 15.56 for sertraline plus exposure, 14.12 for sertraline, and 15.91 for exposure plus placebo. These scores may change a little bit after correction for participants who withdrew from the trial. I doubt that any of these scores differs significantly from each other or from placebo. By no means is it true that 'Exposure therapy given alone is more effective in the long term than when given in combination with sertraline'. The opposite is the case: it takes 1 year for the exposure patients to reach the level of improvement that the sertraline and the combination patients have already reached after half a year. Perhaps the patients treated with exposure only showed further improvement during the 'treatment-free' follow-up period because one-fifth of them now received treatment with selective serotonin reuptake inhibitors. Remarkably, there was no deterioration in the sertraline groups on the primary efficacy measures, despite the fact that only one-fifth of this group remained on medication.

I have calculated a Bonferroni-corrected critical *P*-value of 0.0073 when seven scales are used. Thus, all *P*-values $<0.05$ and $<0.01$ given in the paper may be not significant.

I would suggest that the authors analyse their primary efficacy measures and reinterpret their data.

### *Declaration of interest*

B.B. is or has been a speakers' bureau participant with Aventis, AstraZeneca Pharmaceuticals, Bayer AG, Boehringer-Ingleheim GmbH, Bristol-Myers-Squibb, Eli Lilly and Company, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Meiji-Seiko Pharmaceuticals, Novartis Pharmaceuticals Corp., Organon, Pfizer Inc., Roche, Sanofi-Synthélabo, Solvay, and Wyeth Pharmaceuticals.

**Blomhoff, S., Haug, T. T., Hellstrøm, K., *et al* (2001)** Randomised controlled general practice trial of sertraline, exposure therapy and combined treatment in generalised social phobia. *British Journal of Psychiatry*, **179**, 23–30.

**Haug, T. T., Blomhoff, S., Hellstrøm, K., *et al* (2003)** Exposure therapy and sertraline in social phobia: 1-year follow-up of a randomised controlled trial. *British Journal of Psychiatry*, **182**, 312–318.

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**Author's reply:** The primary efficacy measures from our paper about treatment effect at week 24 (Blomhoff *et al*, 2001) are reported in the method section of the paper about the follow-up study (Haug *et al*, 2003). In the pairwise comparisons, combined sertraline and exposure and sertraline alone were significantly superior to placebo, while a non-significant trend towards increased efficacy of exposure alone compared with placebo was reported.

The four study groups had a significant reduction in scores on all social phobia scales from baseline to follow-up. Furthermore, there was no significant difference in scores on primary efficacy measures between the active treatment groups in any of the time-point analyses between week 0 and week 24. In the follow-up analyses we were therefore mainly interested in the changes after cessation of treatment. For the exposure group and the placebo group there was a further improvement in scores on social phobia from week 24 to week 52 and the changes on several of the subscales were highly significant. On SF–36, which demonstrates changes in a more global functioning, there was a significant improvement for the exposure alone and the placebo groups, while there was a significant deterioration in both the sertraline-treated groups. Changes in scores on other social phobia scales for the sertraline-treated groups were non-significant, but there was a tendency towards deterioration (Tables 1 and 2, pp. 314–315). We agree that the changes in sertraline-treated groups during the follow-up period were marginal. However,



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