undoubtedly wise, but measurement of plasma TCA levels is also a sensible precaution, particularly in the elderly.

Our own experience of combining SSRIs with TCAs such as desipramine and lofepramine has also been encouraging, although sadly the 100% success noted by the authors has eluded us. An adverse effect we have sometimes encountered when combining SSRIs and TCAs has been an increase in agitation and restlessness. Such reactions are important to recognise in depressed patients and we were therefore interested to note that a similar reaction may have occurred in one of the authors' reported cases. At present we believe that combined SSRI–TCA treatment should be reserved for patients who do not respond to lithium augmentation of first-line antidepressant treatment. However, a significant number of patients who do not respond to the latter approach may be helped by subsequent combination of SSRIs and TCAs.

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SIR: I read with interest the article by Seth *et al* (*Journal*, October 1992, **161**, 562–565). They concluded that the combination therapy with nortriptyline and a 5-HT reuptake inhibitor was more effective than individual therapies alone. From their case descriptions, however, I could not find the evidence that the effect of nortriptyline alone was assessed sufficiently before the combination. Moreover, plasma nortriptyline levels in their patients (118 µg/l in Case 4, 68 µg/l in Case 7, and 104 µg/l in Case 8) were within the reported therapeutic range (50–139 µg/l by Åsberg *et al*, 1971; 50–175 µg/l by Kragh-Sørensen, 1973). Thus, there is a possibility that the improvement of their patients was due to nortriptyline alone despite the combination with other drugs.

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AUTHORS' REPLY: Professor Terao raises the issue that nortriptyline alone could have produced the beneficial effect and this was not assessed sufficiently. This was an open clinical case study where patients were treated empirically without study design. As most patients had been on tricyclic antidepressants, which act on many neurotransmitter systems, including down-regulation of beta receptors (Cowen, 1990), and as clinically greater efficacy for nortriptyline compared with other tricyclics has not been shown (Mandells, 1968), it is unlikely that nortriptyline alone could have produced the benefit. We still, however, acknowledge the issue raised by Professor Terao and concluded in our paper that a double-blind clinical trial was necessary.

Drs Cowen and Power make a number of interesting comments associated with potential side effects when using combination treatment with tricyclics and selective serotonin reuptake inhibitors (SSRIs). Firstly, they acknowledge the point already made that there is a need for a controlled trial to evaluate the effect of combination treatment in patients who are unresponsive to first-line antidepressant medication.

The second part concerns pharmacokinetic interaction between SSRIs and tricyclics and we would endorse the view that serum levels of tricyclic antidepressants should be monitored. We would also recommend that, particularly in the elderly, blood pressure should also be monitored, as in our experience a few patients have developed postural hypotension requiring lowering of the tricyclic dose.

Thirdly, they raised the issue of the combination treatment producing an increase in agitation and restlessness in some patients, and indeed this has also been our experience. It is, however, notable that SSRIs alone can produce a similar side-effect and, indeed, occasionally a 'serotonergic crisis'. As