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

https://doi.org/10.1192/S0007125000180237 Published online by Cambridge University Press

lithium can enhance the effect of SSRIs this must also be clinically monitored when used in combination. With regards to our success rate, compared with the authors, this may reflect clinical heterogeneity of the depressed populations being treated (Leonard, 1992). It is still inexplicable why some patients respond to a combination of a broad spectrum tricyclic antidepressant and an SSRI, while others respond to receptor-specific antidepressants, such as nortriptyline and desipramine in combination with an SSRI.

The final point made by Drs Cowen and Power recommending that the combination treatment should be reserved for those who do not respond to lithium augmentation of first line antidepressant treatment, is a prudent approach based on our current knowledge.

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Incidence and epidemiology of schizophrenia in Denmark

SIR: I write in response to the interesting paper by Munk-Jørgenson & Mortensen (*Journal*, October 1992, **161**, 489–495). The authors examine the age-standardised rates of patients admitted to Danish psychiatric hospitals for the first time from 1969 to 1988 and who were diagnosed schizophrenic at least once during this period. They found a reduction of 50% in first-admission schizophrenics. This change is all the more remarkable since day patients were included in the statistics from 1975 onwards.

As they rightly point out, the method utilised will reduce the likelihood that these changes are due to alterations of diagnostic practices, such as a possible growing reluctance to diagnose schizophrenia at the time of first admission. They conclude, however, that the most likely explanation for the change relates to a reduction during the study period of 43% of Danish in-patient beds. There are decreasing first-ever admissions concomitantly in all other diagnostic groups except alcohol-related illnesses and unspecified psychotic states. The authors cite Cooper *et al* (1987), whose study found that 10% of Nottingham schizophrenics were never admitted to hospital over a two-year period, in support of their contention. Their own study, however, looks at a longer period, deals with either admission or day patient attendances, and seeks to explain a reduction of 50%.

As in previous studies, the authors seem reluctant to grasp the nettle and conclude that the incidence of schizophrenia is possibly declining (Eagles, 1987). The fact that the milder categories of illness are declining in frequency of first admissions may well relate to changes in admission policy, but also relate to the fact that psychotic illnesses as a whole are becoming milder (Eagles *et al*, 1988) given that one adopts a continuum model of psychosis, such as that espoused by Crow (1986).

It would be instructive to have information about the extent to which the Danish bed reduction comprises acute psychiatric beds. If the bed reduction mirrors that in the UK, then it has been largely of long-stay beds, that is, not the type of beds which would be occupied by first-admission schizophrenic patients. If the reduction in numbers of new schizophrenic patients was due to the 'squeeze' due to falling bed numbers, it is difficult to explain why the numbers of patients with alcohol-related illnesses (surely much more readily treated as out-patients than schizophrenics) have failed to show a concomitant fall.

Finally, the authors note that there are 5314 newly diagnosed male schizophrenic patients compared with only 3254 females. This is an interesting gender disparity in view of the possibility that narrowly defined schizophrenia may indeed be less common among females (Lewis, 1992); this, if confirmed, could constitute an important clue in the search for the causes of the disorder.

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https://doi.org/10.1192/S0007125000180237 Published online by Cambridge University Press