magnetic resonance, so that subtle differences in outcome can be detected.

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Lithium, Imipramine and Hydroxytryptophan in Resistant Depression

SIR: Hale *et al* (*Journal*, August 1987, **151**, 213–217) reported "the unique efficacy of the triple combination of lithium, clomipramine, and tryptophan" in seven endogenous depressive patients resistant to several other forms of treatment. One of these patients had previously been treated with imipramine and lithium, and another with imipramine and tryptophan, but without success. I would like to report the case studies of two patients with major depression who did not respond satisfactorily to standard doses of imipramine plus hydroxytryptophan (OH-try), but readily and completely did so when lithium was added.

Case reports: (i) Mr G. L., a 48-year-old married man, was referred to our out-patient service for a 16-month depressive episode. His mother committed suicide during a depressive episode at the age of 39. The patient had a 23-year history of depressive recurrences, with a mean inter-episode interval of 3 years. In his previous episodes he had responded adequately to standard antidepressant treatments. During the present episode, however, he failed to respond to several antidepressants (amitriptyline, nortriptyline, mianserine, amineptine, nomifensine and tranylcypromine) at doses and for periods similar to those of previous episodes. When examined, he was a DST non-suppressor and his Hamilton score was 21. Imipramine (150 mg/day) plus OH-try (300 mg/day) was administered. During the following 6 weeks, a slight but unsatisfactory improvement was evident (Hamilton score = 16). Then, lithium carbonate (900 mg/day) (plasma level 0.41 mEq/l) was added. His mood substantially improved by the following week, with a Hamilton score drop to 5. He recovered completely and returned to his job during the following two weeks.

(ii) Mr D. D., aged 20, was referred to our out-patient service during his military service because of a severe depressive episode and manifest suicidal thoughts. He was a DST non-suppressor, and his Hamilton score was 31. He was administered imipramine (75 mg/day) for two weeks, which was then increased to 150 mg/day plus OH-try (400 mg/day) for the following four weeks. During this time his mood did not change substantially, and the Hamilton score decreased by no more than 20%. Lithium carbonate (900 mg/day) (plasma level 0.52 mEq/l) was added, and an improved mood was immediate. By the following week his Hamilton score had decreased by 80%, and he had a complete recovery during the subsequent two weeks.

These case studies suggest that: (a) the administration of lithium and OH-try is also synergistic with imipramine, and not only with clomipramine as Hale *et al* seem to suggest; (b) the addition of lithium to a tricyclic antidepressant and OH-try show that it is clinically efficacious in a period of time shorter than that of other drug treatments for drug-resistant depressives; (c) the clinical efficacy and rapidity of action of this combined treatment manifests itself even without administration of maximal doses of the tricyclic antidepressant. This might depend on the fact that tryptophan is hydroxylated and thus bypasses the limiting step of tryptophan hydroxylation and is readily metabolised to serotonin by neurons.

This combined treatment might be considered one of first choice in the management of drug-resistant major depressive patients. In fact, the canonical increase of the tricyclic antidepressant dose to the point that intolerable side-effects appear generally does not have clinical efficacy until two to three weeks pass. Moreover, this often may be impractical in elderly patients and those particularly sensitive to side-effects. Finally, it would seem to be good clinical practice to avoid the risks associated with the administration of high tricyclic doses unless such doses are an absolute necessity.

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Two-Stage Screening

SIR: We read with interest the paper by Sen *et al* (*Journal*, July 1987, **151**, 33–38) which described the success of the two-stage screening procedure for identifying psychiatric morbidity in primary health clinics in Calcutta (India) and Sao Paulo (Brazil).