Once rarely prescribed because of the fear of severe complications such as hypertensive crises, hyperthermia, and delirium, the monoamine oxidase (MAO) inhibitors have gained renewed interest for the therapy of depressive disorders. On the one hand, it might be due to the fact that prevention through strong dietary precautions has decreased the incidence of adverse reactions\textsuperscript{1,2}; on the other hand, there is evidence that MAO inhibitors may have a unique role in the therapy of many depressed patients who respond poorly to alternative treatments.\textsuperscript{1-4} One aspect of using MAO inhibitors—combining them with tricyclic antidepressants in the treatment of therapy-resistant depression—has always been controversially discussed with regard to its unusual toxicity\textsuperscript{5-7} and efficacy.\textsuperscript{8-12}

Theoretical considerations suggest that such a combined regimen might lead to a more frequent, more rapid, and more pronounced improvement in depressive symptomatology in comparison to a monotherapy. The mechanism, assumed for the possible potentiation of tricyclics by MAO inhibitors, is the combined effect of tricyclic-mediated uptake inhibition and enzyme inhibition following the MAO inhibitor.

The aim of this retrospective study was to obtain detailed information about the safety and efficacy of combined tri/tetracyclic (TCA) and tranylcypromine antidepressant treatment in therapy-resistant depressed inpatients. "Therapy resistant" was defined as at least two unsuccessful single-drug tri/tetracyclic treatments over a period of 3–4 weeks each.

Subjects

A review was made of the charts of all inpatients treated on the combined regimen in the Department of Psychiatry, University of Munich, between January 1977 and June 1981. There were 94 patients; 78 of them were suffering from a depressive episode within a monopolar depression (ICD 296.1), 13 from a depressive episode within a bipolar disorder (ICD 296.3), two from a neurotic depression (ICD 300.4), and one from a depressive syndrome within an organic depression.
Methods

Therapeutic outcome and side effects were measured as described in a previous report.13

Results

In all cases tranylcypromine, in a fixed combination with a small amount (1 mg) of the neuroleptic trifluoperazin (Jatrosom), was used as the MAO inhibitor. The procedure used in all cases for administering the combined TCA–MAO inhibitor treatment was the following: After at least 7 weeks of TCA treatment patients received 10 mg of tranylcypromine, gradually increasing this dosage up to a maximum of 30 mg. The daily dosage of tranylcypromine ranged between 10 and 30 mg with a mean dose of 13 mg/day.

Tranylcypromine was combined with amitriptyline in 37 patients, imipramine in 20 patients, dibenzepine in 14 patients, nomifensine in 6 patients, mianserine in 8 patients, doxepine in 4 patients, chlorimipramine in 2 patients, lofepramine in 2 patients, and maprotiline in 1 patient. Mean daily dose and dosage range of these antidepressants did not differ significantly when comparing single with combined antidepressant treatment. Amitriptyline, for example, was administered as a single drug in a mean daily dose of 179.2 mg with a dosage range of 75–250 mg; in combination with tranylcypromine its mean daily dose was 152.8 mg with a dosage range of 75–250 mg. The mean daily dose of imipramine was 193.3 mg when given as a single drug and increased to a mean daily dose of 222 mg in combined therapy, the dosage range in both treatment groups being 50–300 mg.

As to the efficacy of combined antidepressant treatment, within a mean treatment period of 21.9 days 31% of the patients demonstrated a very good and 37% of the patients a good response to combined treatment, the most effective combination being amitriptyline + tranylcypromine, with a very good therapeutic response in 51% and a good therapeutic response in 27% of the patients, followed by the combination of other tricyclics such as imipramine, doxepine, and dibenzepine + tranylcypromine with a very good or good therapeutic response in about 60% of the patients.

In general, the combined treatment produced a slightly but not significantly lower frequency of side effects (1.56 per treatment) than did the single antidepressant treatments (1.84 per treatment). Combining tranylcypromine with chlorimipramine and nomifensine, however, led to an increase of side effects; in the case of nomifensine this increase was especially due to abnormalities in laboratory parameters and vegetative side effects. A reduction of side effects was seen after combining tranylcypromine with dibenzepine, doxepine, and especially amitriptyline. Combining these drugs produced a lower frequency of all classes of side effects—cardiovascular, central nervous system, vegetative, laboratory, and others—than did single amitriptyline treatment.

Throughout all single drug and combined treatments, close monitoring of patients’ physical status, including vital signs, uncovered no occurrence of a hyperthermic crisis in any patient.

In four of the 94 patients, however, combined TCA–MAO inhibitor had to be discontinued because of other adverse reactions. A 54-year-old woman treated with 150 mg amitriptyline and 10 mg tranylcypromine complained about severe