

antihypertensive drugs, however, may shed some light on the mechanism of action of *d*-amphetamine in the treatment of attention deficit disorder. The results of the metoprolol interaction suggest that the therapeutic effect is, at least in part, mediated by β_1 adrenergic receptors. In addition, the results of the prazosin interaction imply that the central stimulant properties of amphetamine are dependent on α_1 adrenergic receptors.

Regardless of which receptors are involved, this case history demonstrates that the use of *d*-amphetamine is not necessarily contraindicated in the presence of antihypertensive therapy, but antihypertensive drugs may modify the desired clinical effect of *d*-amphetamine in the treatment of attention deficit disorder, residual type.

REFERENCES

1. Wender PH, Reimherr FW, Wood DR: Attention deficit disorder ('minimal brain dysfunction') in adults: a replication study of diagnosis and drug treatment. *Arch Gen Psychiatry* 38:449-456, 1981
2. Wender PH, Reimherr FW, Wood D, et al: A controlled study of methylphenidate in the treatment of attention deficit disorder, residual type, in adults. *Am J Psychiatry* 142:547-552, 1985

PAUL H. WENDER, M.D.
Salt Lake City, Utah

Mania Induced by Gradual Withdrawal From Long-Term Treatment With Imipramine

SIR: The development of mania and fast-cycling bipolar disorder following withdrawal from long-term treatment with a tricyclic antidepressant has been reported in the literature (1, 2). Mirin et al. (2) reported on seven patients who had undergone drug treatment for at least 12 weeks (mean=67.2 weeks, range=12-208 weeks) before stopping treatment. In these patients, manic symptoms persisted for 1-4 weeks.

Here we describe the induction of mania that lasted 6½ months, followed by depression, on discontinuation of 12 years of imipramine therapy in a patient who had a history only of recurrent unipolar major depressive disorder.

Mr. A, a 52-year-old man, had his first episode of endogenous depression at age 25. He developed sadness, anorexia, insomnia, and suicidal ideas; his attempt to jump into a well resulted in an admission to the hospital. He had had no prior psychiatric illness.

A history of endogenous depression was documented in his father, two uncles, grandfather, one brother, and two sisters, but there was no evidence of bipolar illness. He was treated with antidepressants and ECT. For another 12 years he remained completely asymptomatic without drug therapy.

At age 37 he relapsed and attempted suicide by jumping from a roof. He improved while taking a combination of imipramine and diazepam. He continued taking this combination for another 5 months and relapsed following discontinuation of the drugs. He was advised to continue the treatment for a long time. For the next 12 years he continued to take 150 mg/day of imipramine and remained quite stable, attended work and social occasions,

and did not have any attacks of mania or depression. Even 4 years after the death of his attending psychiatrist, he continued to self-medicate with the drugs. His family did not want to risk withdrawing the drugs.

When he attended our clinic, he was advised to begin a gradual withdrawal from the imipramine. He did so over a period of 11 months and discontinued the drug completely. Two days after he stopped taking the medication, he began to experience a marked increase in energy and libido. He started taking an extraordinary interest in local politics. He had rapid speech and inappropriate euphoria. These symptoms continued for 6½ months, and he received no psychotropic medication. The symptoms abated gradually over a period of 2 weeks. One month later he experienced another depressive episode and was treated with a combination of amitriptyline (150 mg/day) and lithium. He remained free of mania and depression during 9 months of follow-up.

To the best of our knowledge, both the 12 years of imipramine treatment and the 6½ months of withdrawal-induced mania are the longest durations reported in the literature. Thus, one can presume that the phenomenon observed is related not only to the withdrawal from tricyclics but to the long-term administration as well.

REFERENCES

1. Jones BD, Steinberg S, Chouinard G: Fast-cycling bipolar disorder induced by withdrawal from long-term treatment with a tricyclic antidepressant. *Am J Psychiatry* 141:108-109, 1984
2. Mirin SM, Schatzberg AF, Creasey DE: Hypomania and mania after withdrawal of tricyclic antidepressants. *Am J Psychiatry* 138:87-89, 1981

RAJEEV GUPTA, M.D.
R.L. NARANG, M.D.
Ludhiana, India

Patient With Chronic and Apparently Treatment-Resistant Dysthymia

SIR: We had an experience that may be of interest concerning patients with chronic and apparently treatment-resistant dysthymias.

Recently we treated Mr. A, a 33-year-old man in good general health, who reported a 20-year history of depression characterized by episodic dysphoria, continuous fatigue, and frequently disturbed sleep. His sleep problems included frequent morning hypersomnia and sleep-onset insomnia as well as a progressive phase delay of the sleep-wake cycle (falling asleep and awakening at successively later times). Anhedonia, apathy, and social withdrawal were associated symptoms; a dexamethasone suppression test revealed borderline nonsuppression of plasma cortisol (5.9 $\mu\text{g}/\text{dl}$ at 4:00 p.m.). The patient met *DSM-III* criteria for dysthymic disorder.

The chronic course of the patient's dysthymia and the unremitting, cross-situational quality of his fatigue and sleep problem suggested the presence of an endogenous or biological disturbance. Nevertheless, the patient had undergone unsuccessful trials with many antidepressants, including lithium and methylphenidate, without experiencing a positive clinical response. Surprisingly, some benefit was obtained with the monoamine oxidase inhib-

itor (MAOI) isocarboxazid, even though other MAOIs had not helped. While taking a dose of 20 mg t.i.d., the patient reported a substantial decrease in dysphoria (an elevation of mood from predominantly depressed to neutral) accompanied by increased motivation and social interest; there were no noteworthy side effects. The chronic fatigue and sleep problems, however, remained unaffected. To alleviate these symptoms, we tried various other tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, and doxepin) in combination with the isocarboxazid (at 60 mg/day). Only the addition of doxepin (150 mg h.s.) yielded a positive additional clinical effect (periods of mild euphoria and some reduction in sleep latency) but, again, without affecting daytime fatigue; no side effects developed. Over six weeks, the addition of amoxapine (50 mg h.s.) in combination with isocarboxazid (60 mg/day) resulted in enhanced mood, shorter mean sleep time (from 8.5 hours to 7.5 hours), elimination of sleep-onset insomnia, and elimination of phase delay; again, no major side effects developed. Blood pressure was monitored weekly throughout the combination trials and never exceeded 130/80 Hg. While some improvement in energy level did occur, daytime fatigue remained a problem, as did the patient's impression of not having gotten sufficiently restful sleep. Higher doses of amoxapine resulted in initial amphetamine-like energy, greatly reduced sleep times, nocturnal awakenings, and vivid, disturbing dreams, followed by eventual daytime exhaustion as a result of insufficient sleep.

When conventional drug regimens have been unsatisfactory, the physician is obliged to assess the potential risks and benefits of less conventional approaches. Potential risks include not only pharmacological side effects and toxicity of unusual drug doses or combinations but the risk of avoiding psychotherapeutic work while pursuing ineffective regimens of medications. Potential benefits may arise from the presumed biological individuality of treatment-resistant patients; this may encourage additional trials of antidepressant medications even after repeated failures.

SHERWIN J. HARRIS, M.D.
MARK PARENT, M.A.
Great Neck, N.Y.

Side Effects of the New Antidepressants

SIR: Three new antidepressants have recently been marketed in this country: maprotiline, amoxapine, and trazodone. All have been found to have antidepressant efficacy equivalent to that of the tricyclic antidepressants, so it is claims of reduced side effects that would warrant their use as first-line antidepressants. However, the secondary amine tricyclics (e.g., desipramine and nortriptyline) may also have fewer side effects than the primary amines imipramine and amitriptyline (1). We therefore reviewed the available literature to determine if there is evidence that the new antidepressants have fewer side effects than the secondary amine, and not just the primary amine, tricyclics.

In the case of maprotiline, the first of the new antidepressants to be marketed, a 1977 review by Pinder et al. (2) summarized 33 studies comparing maprotiline to a tricyclic (19 comparisons with amitriptyline, 13 with imipramine, and only one with a secondary amine, nortriptyline). This review found maprotiline to have fewer side effects than

either imipramine or amitriptyline, but, on the basis of the one study, found it to have comparable side effects to nortriptyline. Computer searches of more recent literature found no additional comparisons involving a secondary amine.

The situation with trazodone and amoxapine is similar. Trazodone has fewer side effects than either imipramine or amitriptyline (3), but we found only one study comparing trazodone to a secondary amine, desipramine (4); this study found equivalent efficacy but did not compare side effects. We have not located any comparison between amoxapine and a secondary amine tricyclic (5).

As is not uncommon with new drugs, the three new antidepressants, since approval by the Food and Drug Administration, have been found to have additional side effects (or higher than expected frequencies of side effects). Maprotiline may lower the seizure threshold more than tricyclics do, amoxapine apparently has neuroleptic effects and neuroleptic side effects with the potential for inducing tardive dyskinesia, and trazodone has been reported to have cardiac side effects and to be potentially arrhythmogenic in patients with preexisting cardiac disease.

Thus, there is no convincing evidence that the three new antidepressants have fewer side effects than the secondary amine tricyclics, which have been used for 20 years. Given this, and the apparently equivalent efficacy, there is little clinical rationale for using any of these new drugs as a first treatment; unknown risks are inevitably greater with newer drugs. Nevertheless, valuable theoretical and clinical advances can take place with the judicious use of these agents.

REFERENCES

1. Davis JM: Antidepressant drugs, in *Comprehensive Textbook of Psychiatry*, 3rd ed. Edited by Kaplan HI, Freedman AM, Sadock BJ. Baltimore, Williams & Wilkins, 1980, pp 2298-2299
2. Pinder RM, Brogden RN, Spling TM, et al: Maprotiline: a review of its pharmacological properties and therapeutic efficacy in mental depressive states. *Drugs* 13:321-352, 1977
3. Gershon S, Rickels K, Silvestrini B (eds): *Trazodone: A New Broad-Spectrum Antidepressant*. Amsterdam, Excerpta Medica, 1980
4. Agnoli A, Piccione M, Casacchia M, et al: Trazodone versus desipramine, in *Modern Problems of Pharmacopsychiatry*, vol 9. Edited by Ban TA, Silvestrini B. Basel, Karger, 1974, pp 190-198
5. Ban TA: Amoxapine and viloxazine: review of the literature with special reference to clinical studies. *Psychopharmacol Bull* 15:22-25, 1979

JEFFREY A. MATTES, M.D.
Belle Mead, N.J.

An Early "Study" of Seasonal Depression

SIR: In 1898 the *Belgica* and her crew of 19 were trapped in the Antarctic ice pack, "gripped fast as a fly in amber," for 347 days. They were the first to experience the rigors of an Antarctic winter, with its 68 continuous days of darkness, until the sun again appeared above the horizon "like a small withered orange" (1).

The ship's doctor, Frederick Cook, recognized both the adverse effect of darkness on the well-being of the crew ("Gradually the members of the expedition became affected, body and soul, with langour") and the beneficial effects of light ("Bright artificial lights relieve this to some extent; but