

ferred from headaches, nausea, vomiting, abdominal discomfort, and agitation. At that time, 10 mg of paroxetine was given to Ms. A, with resolution of all symptoms. She was placed back on a regimen of paroxetine without further symptoms.

It is interesting to note that because of the lack of side effects of the initial medication, this patient was not suffering from serotonin abnormalities due to the blockade by sertraline. Symptoms of withdrawal have been reported to manufacturers of selective serotonin reuptake inhibitors (1), although information is lacking (2). There are some data on paroxetine withdrawal from the Committee on Safety of Medicines (1, 3).

Symptoms in this patient may, in fact, represent paroxetine withdrawal and would suggest the need for tapering of this medication. Although fluoxetine has been reported to the manufacturer to cause a withdrawal syndrome (personal communication from Eli Lilly Research Laboratories), it is theoretically less likely because of the very long plasma half-life of fluoxetine.

This potential withdrawal syndrome should be kept in mind with any abrupt discontinuation of a selective serotonin reuptake inhibitor as well as with the hospitalization of patients who take these medications and develop the syndrome.

## REFERENCES

1. Committee on Safety of Medicines: Dystonia and withdrawal symptoms with paroxetine (Seroxat). *Current Problems in Pharmacovigilance*, Feb 1993, p 1
2. Sindrup SH, Gram LF, Broesen K, Eshoj O, Mogensen EF: The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. *Pain* 1990; 42:135-144
3. Choo V: Paroxetine and extrapyramidal reactions. *Lancet* 1993; 341:624

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### Late-Onset Psychotic Depression Associated With Carbaryl Exposure

TO THE EDITOR: We report for the first time major depression with psychosis precipitated by repeated exposure to carbaryl, a reversible cholinesterase inhibitor.

Ms. A, a 69-year-old married woman without personal or family history of psychiatric illness, was admitted to an acute-care, geriatric psychiatry inpatient service. Six weeks before admission, her neighbor began spraying his yard once a week for 4 consecutive weeks with an insecticide that contained carbaryl. Two weeks before her admission, Ms. A noted dead animals in her yard, erratic behavior in her pets, and hypersomnia in her husband. Ms. A herself experienced diarrhea, abdominal cramps, anorexia, nausea, headaches, poor concentration, muscle weakness, malaise, confusion, lightheadedness, diaphoresis, and greater lacrimation. She also developed persistent tremor, anxiety, dysphoria, crying spells, and persecutory and nihilistic delusional ideation. She lost 10 pounds and complained of fatigue and insomnia. She developed auditory hallucinations and was admitted to a local hospital. Results of a physical examination, computed tomography scan of the head, and routine investigations were unremarkable. Ms. A was

treated with a regimen of paroxetine and thioridazine but did not improve.

After 4 days Ms. A was transferred to a psychiatric hospital; she was cognitively intact. The paroxetine and thioridazine treatment was discontinued, and she received a regimen of fluphenazine and nortriptyline. Her psychotic symptoms cleared, and by the fourth week of hospitalization her depressive syndrome had resolved (Hamilton depression scale score of 6). Plasma pseudocholinesterase activity was 3.1 U/ml and 3.3 U/ml during the third and fourth hospital weeks, respectively (normal level=3.4-6.5 U/ml).

Carbaryl intoxication results from ingestion, inhalation, or percutaneous absorption. Carbaryl undergoes rapid metabolism after acute exposure (half-life of 40 minutes). Repeated exposure may have effects similar to those of "irreversible" organophosphate cholinesterase inhibitors (1, 2). Individuals vary widely in the dose of carbaryl associated with toxicity (3, 4). Metabolism is slower in women and in older adults (2, 4).

This patient showed evidence of cholinergic overstimulation at peripheral muscarinic receptors, i.e., dyspnea, anorexia, nausea, diarrhea, and lacrimation. Fatigue, depression, and poor concentration and memory have been linked to central antimuscarinic effects. Her muscle weakness was consistent with cholinergic overstimulation at peripheral nicotinic receptors.

Abnormal central cholinergic tone may be involved in the pathophysiology of affective disorders (5). Cholinesterase inhibitors induce or worsen depression in psychiatric patients (6), decrease manic symptoms (6), and precipitate dysphoria in healthy subjects (7).

Neuropsychiatric sequelae of carbaryl exposure include aggression (8), memory loss (1), progressive muscle weakness (2), and peripheral neuropathy (9). Major depression (1, 8, 10) and psychosis (1, 10) have been reported after organophosphate, but not carbaryl, poisoning. Major depression with psychotic features has not been described following either organophosphate or carbaryl poisoning.

Carbaryl increases avian brain dopamine synthesis (11). Dopaminergic dysregulation has been implicated in psychotic symptoms (12).

The patient had low plasma pseudocholinesterase activity 5-6 weeks after the last carbaryl exposure. Plasma pseudocholinesterase activity may indirectly reflect synaptic cholinesterase activity (13). Although activity before carbaryl exposure was not known in this case, activity normalizes rapidly after acute carbaryl exposure, and sustained low exposure to organophosphates does not tend to alter plasma pseudocholinesterase activity (1, 2). This patient may have been vulnerable to carbaryl on the basis of demographic factors that influence pharmacokinetics and low baseline cholinesterase activity.

## REFERENCES

1. Branch RA, Jacqz E: Subacute neurotoxicity following long-term exposure to carbaryl. *Am J Med* 1986; 80:741-745
2. Branch RA, Jacqz E: Is carbaryl as safe as its reputation? Does it have a potential for causing chronic neurotoxicity in humans? *Am J Med* 1986; 80:659-664
3. Branch RA: Is carbaryl as safe as its reputation? (letter). *Am J Med* 1987; 83:1169
4. Ward S, Branch A: Is carbaryl as safe as its reputation? (letter). *Am J Med* 1986; 81:1125-1126

5. Janowsky DS, El-Yousef MK, Davis JM: Acetylcholine and depression. *Psychosom Med* 1974; 36:248-257
6. Janowsky DS, El-Yousef MK, Davis JM, Sekerke HJ: A cholinergic-adrenergic hypothesis of mania and depression. *Lancet* 1972; 2:632-635
7. Hasey G, Hanin I: The cholinergic-adrenergic hypothesis of depression reexamined using clonidine, metoprolol, and physostigmine in an animal model. *Biol Psychiatry* 1991; 29:127-138
8. Devinsky O, Kernan J, Bear DM: Aggressive behavior following exposure to cholinesterase inhibitors. *J Neuropsychiatry Clin Neurosci* 1992; 4:189-194
9. Gershon S, Sydney MB, Shaw FH: Psychiatric sequelae of chronic exposure to organophosphorus insecticides. *Lancet* 1961; 1: 1371-1374
10. Dille JR, Smith PW: Central nervous system effects of chronic exposure to organophosphate insecticides. *Aerospace Medicine* 1964; 35:474-478
11. Cranmer MF: Carbaryl: a toxicological review and risk analysis. *Neurotoxicology* 1986; 7:247-328
12. Haracz JL: The dopamine hypothesis: an overview of studies with schizophrenic patients. *Schizophr Bull* 1982; 8:438-469
13. Namba T, Nolte CT, Jackrel J, Grob D: Poisoning due to organophosphate insecticides: acute and chronic manifestations. *Am J Med* 1971; 50:475-492

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### Ephedrine-Induced Mania From an Herbal Diet Supplement

TO THE EDITOR: Potent sympathomimetic drugs, such as ephedrine and phenylpropanolamine, are widely available in over-the-counter formulations and in so-called food supplements (1). These products are sold as decongestants and dieting aids but may also be marketed as stimulants. Ephedrine is present in literally dozens of products, often in the form of an extract of the main plant source: *E. sinica* (Ma-huang). I recently evaluated a man who developed a manic episode associated with use of an herbal preparation that contained unspecified amounts of Ma-huang.

Mr. A, a 45-year-old man with no history of psychiatric illness or substance abuse, was brought to the emergency room by his wife, who reported that Mr. A had undergone personality and behavior changes in the past month. For 2 months Mr. A had been taking a daily herbal diet supplement for weight loss. After several weeks of using greater amounts, he began to get restless and could not sleep. He seemed irritable to his family but reported improved mood. His work became so disorganized that his supervisor asked him to take a leave of absence. He had pressured speech and began to be preoccupied with religious themes. He argued with his minister about biblical meanings and the coming "rapture." He became so uncharacteristically aggressive and verbally abusive that his wife insisted on a medical examination.

A limited physical examination and laboratory studies revealed only hypertension. The emergency room physician suggested discontinuation of the herbal capsules, which were labeled as Ma-huang. A regimen of trazodone, 50 mg/day, was prescribed as a sedative. Mr. A's wife said that by the third day, with several nights' sleep, Mr. A was himself again. When I examined him on the fourth day, I found no evidence of mood or thought disorder.

His wife reported no similar episodes in 20 years of marriage. She did say he had moody periods, which she attrib-

uted to work stress, and several minor "spending sprees" of little consequence. He had no major medical problems and took no prescribed or over-the-counter medications. Family history included a possibility of bipolar illness in the father, who had manic-like episodes and abused alcohol but was never diagnosed or treated. Mr. A discontinued trazodone treatment after 1 week. He showed no evidence of mood instability after 1 year of follow-up.

Intoxication with ephedrine can occur in the context of incidental exposure for persons who take formulations for weight loss or other health benefits or in the context of stimulant abuse by drug-seeking persons (2). Chronic ephedrine use can produce delusional disorders as well as manic conditions that may be more likely in predisposed individuals (3-5).

I urge physicians who are evaluating persons with recent onset of psychotic or manic symptoms to consider ephedrine intoxication in their differential diagnosis and to ask specifically about use of diet supplements that contain Ma-huang.

### REFERENCES

1. Lake CR, Quirk RS: CNS stimulants and the look-alike drugs. *Psychiatr Clin North Am* 1984; 7:689-701
2. Dougherty RJ: Pseudo-speed: look-alikes or pea-shooters. *NY State J Med* 1982; 1:74-75
3. Herridge CF, a'Brook MF: Ephedrine psychosis (letter). *Br Med J* 1968; 2:160
4. Whitehouse AM, Duncan JM: Ephedrine psychosis rediscovered. *Br J Psychiatry* 1987; 150:258-261
5. Lake CR, Tenglin R, Chernow B, Holloway HC: Psychomotor stimulant-induced mania in a genetically predisposed patient: a review of the literature and report of a case. *J Clin Psychopharmacol* 1983; 3:97-100

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### Dystonia and Drug-Induced Hepatitis in a Patient Treated With Clozapine

TO THE EDITOR: Clozapine has a low prevalence of extrapyramidal side effects (1); in particular, no acute dystonia has been reported (2). It may, however, produce abnormal liver function test results in up to one-third of patients (3). Two cases of clozapine-induced hepatitis (with prominent transaminase elevation) have previously been described (4, 5). We report a case of drug-induced dystonia and hepatitis in a woman treated with clozapine.

Ms. A, a 30-year-old woman with a 5-year history of paranoid schizophrenia, developed oculogyric crises and a dose-dependent transaminase elevation while she was receiving clozapine. She was hospitalized for management of persistent auditory hallucinations and persecutory delusions, despite successive trials of chlorpromazine, haloperidol, and trifluoperazine (1000 mg/day of chlorpromazine equivalents), each in conjunction with weekly regimens of fluphenazine decanoate, 37.5 mg i.m.

Ms. A had been an intravenous opiate abuser several years earlier, and 5 months before admission she was found to be hepatitis C seropositive (she was hepatitis A and B and HIV seronegative). There had been persistent mild elevation of alanine aminotransferase (ALT) to a level of 67 U/liter over the preceding 2 years (possibly the effect of hepatitis C or conventional neuroleptic treatment), but