Letters to the Editor

Serotonin and Depression in Frontal Lobe Dementia

TO THE EDITOR: Frontal lobe dementia is a presenile dementia (1, 2) in which the prominent initial symptoms are psychiatric and behavioral with relative preservation of memory, spatial orientation, and performance. Depressive symptoms have been reported as transient (1) or, in contrast, as part of a progressive decline with minimal response to treatment (2). We present two cases of severe depressive illness occurring in the context of frontal lobe dementia in which there was sustained improvement with the combination of lithium and a selective serotonin reuptake inhibitor.

Mr. A was a 44-year-old man with a 15-year history of episodes of anxiety, depression, and self-harm. Treatment had included a variety of antidepressant regimens and two courses of ECT, which resulted in variable improvement that was not sustained. In the year before admission, he showed greater self-neglect and behavioral disturbance, which included self-harm, fecal smearing, and falsely claiming to have committed crimes. On examination he was severely depressed and agitated with nihilistic delusions. After neurological examination, brain scans (computerized tomography [CT] and single photon emission computed tomography [SPECT]), and neuropsychological testing, he was diagnosed as having frontal lobe dementia. ECT produced a dramatic but temporary improvement, and sustained improvement was achieved only with a combination of fluoxetine and lithium. After 1 year he remained euthymic and without behavioral problems, but he lacked motivation and needed some prompting with daily living activities. Readministration of the neuropsychological tests showed no improvement in cognitive function in contrast to the marked clinical improvement.

Mr. B was a 53-year-old man who had suffered a depressive illness in his 30s. After 1 year of a progressive depressive condition, he presented to the hospital with greater muteness and retardation and delusions of persecution, disease, and guilt. Over the next 2 years he had four courses of ECT and many different antidepressant regimens that were combined on occasion with neuroleptics, lithium, and triiodothyronine. His psychotic symptoms improved, but there was minimal effect on his mood and functioning. After neurological referral a diagnosis of frontal lobe dementia was made on the basis of clinical examination and neuropsychological tests, although CT and SPECT brain scans revealed no abnormality. He failed to settle into a specialist nursing home because of increasing agitation and behavioral disturbance. He was treated in the hospital with the previously untried combination of paroxetine and lithium, which led to gradual improvement over the next 6 months.

Over the following year he remained euthymic with good self-care and some regained interests, but he still lacked motivation and spontaneity. Readministration of the neuropsychological tests showed improvement in cooperation and memory tasks but not in tests of frontal lobe function. A SPECT brain scan revealed patchy deficits in the frontal and parietal cortex areas.

After previous treatment resistance or rapid relapse, both patients finally showed a sustained response to the combination of lithium and a selective serotonin reuptake inhibitor. Frontal lobe damage has been associated with reduced brain serotonin function (3), and we suggest that the efficacy of this treatment combination is due to a potent enhancement by lithium of the serotonergic effect of the selective serotonin reuptake inhibitor. This enhancement increases serotonin release and postsynaptic serotonin$_1$ receptor function (4). This combination may therefore be particularly indicated for depressive disorder that occurs in conditions with frontal lobe damage.

REFERENCES

1. Gustafson L: Frontal lobe degeneration of non-Alzheimer type. II. Clinical picture and differential diagnosis. Archives of Gerontology and Geriatrics 1987; 6:209–223
2. Neary D, Snowden JS, Northen B, Goulding P: Dementia of the frontal lobe type. J Neurol Neurosurg Psychiatry 1988; 51:353–361
3. van Woerkom TC, Teelken AW, Minderhous JM: Difference in neurotransmitter metabolism in frontotemporal-lobe contusion and diffuse cerebral contusion (letter). Lancet 1977; 1:812–813
4. Wood AJ, Goodwin GM: A review of the biochemical and neuropharmacological actions of lithium. Psychol Med 1987; 17:579–600

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A Possible Paroxetine Withdrawal Syndrome

TO THE EDITOR: I would like to report a case of a 40-year-old female patient who may have undergone withdrawal after the abrupt discontinuation of paroxetine.

Ms. A had been maintained on a regimen of paroxetine, 20 mg/day, for approximately 5 weeks. Because of adverse effects on her libido, she elected to switch to sertraline therapy. After discontinuation of paroxetine treatment, she was given a regimen of sertraline, 50 mg/day. During the ensuing 3 days, she developed headaches, nausea, vomiting, abdominal discomfort, and agitation.

The symptoms were initially felt to be secondary to the institution of sertraline so the medication was discontinued after 1 week. Ms. A was restarted on a regimen of paroxetine, 20 mg/day, with resolution of all symptoms. She discontinued paroxetine treatment, and after 3 days she suf-

fered 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, Brosen 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