association between smoking and schizophrenia: 1) experimental demonstration of causality, and 2) biological plausibility. Experimental demonstration is not feasible. Biological plausibility is the weakest of Hill's criteria because, as he pointed out, it depends on the biological knowledge of the day, and we must not await knowledge of the biological mechanism involved in causation before deducing that causation exists. Causality has been demonstrated between smoking and depression, although the mechanism remains speculative (15). We assess plausibility by analogy and note the causal connection between stimulant, appetite suppressant drugs such as amphetamines and hallucinatory, delusional psychoses (16). Nicotine, of course, is a cerebral stimulant and an appetite suppressant.

Although schizophrenic disorders are now formally defined in terms of symptoms (17), many psychiatrists still conceptualize schizophrenia as Kraepelin's "well-characterized . . . disease . . . a single morbid process" (18). It is then easy to postulate that an innate predisposition to smoking might simply co-exist with a predisposition to schizophrenia. The "cause" of schizophrenia has defied discovery for so long that researchers who assume that the state is unitary understandably also assume that, whatever the cause may be, it will prove both complex and abstruse. This is an assumption based upon an assumption (19)—too flimsy to obscure the obvious: if a disability is frequently preceded by exposure to a particular toxin, it is correct to say that the toxin is not necessarily causal; at the same time, however, this possibility is the first explanation that should arise.

Yet in the literature, the hypothesis that smoking may contribute to the causation of schizophrenia is not mentioned or commands only passing attention. This omission testifies to the power that traditional received authority continues to hold over researchers and irrationally deprives us of a potential preventive strategy.

References

1. Lohr JB, Flynn K. Smoking and schizophrenia. Schizophr Res 1992;8:93–102.
2. McEvoy JP. Smoking and schizophrenia. Drug Development Research 1996;38:263–6.
3. de Leon J. Smoking and vulnerability for schizophrenia. Schizophr Bull 1996;22:405–9.
4. Goff DC, Henderson DD, Amico E. Cigarette smoking in schizophrenia: relationship to psychopathology and medication side effects. Am J Psychiatry 1992;149:1189–94.
5. Hare E. Schizophrenia as a recent disease. Br J Psychiatry 1988;153:521–31.
6. Hare E. Aspects of the epidemiology of schizophrenia. Br J Psychiatry 1986;149:554–61.
7. Dohan FC. Wartime changes for hospital admissions for schizophrenia. Acta Psychiatr Scand 1966;42:1–23.
8. Milmore BK, Conover AG. Tobacco consumption in the United States, 1880-1955. Public Health Monograph No.45;1956:107–11.
9. Jaffe JH. Drug addiction and drug abuse. In Gilman AG, Rall TW, Nies AS, Taylor P, editors. The pharmacological basis of therapeutics. 8th ed. New York: McGraw Hill; 1993. p 545–8.
10. Joyce PR. Changing trends in first admissions and readmissions of mania and schizophrenia in New Zealand. Aust N Z J Psychiatry 1987;21:82–6.
11. Bland RC. Clinical features of affective disorders. I: Diagnosis, classification, rating scales, outcome and epidemiology. In: Dewhurst WG, Baker GB, editors. Pharmacotherapy of affective disorders: theory and practice. London: Croom Helm; 1985.
12. Salem JE, Kring AM. The role of gender differences in the reduction of etiological heterogeneity in schizophrenia. Clin Psychol Rev 1998;18:795–819.
13. Albus M, Maier W. Lack of gender differences in age at onset in familial schizophrenia. Schizophr Res 1995;18:51–7.
14. Hill AB. The environment and disease: association or causation? Proc Roy Soc Med 1965;58:295–300.
15. Goodman E, Capitman J. Depressive symptoms and cigarette smoking among teens. Pediatrics 2000;106:748–55.
16. Beamish P, Kiloh LG, Psychoses due to amphetamine consumption. J Ment Sci 1960;10:337–43.
17. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington (DC.): American Psychiatric Association; 1994.
18. Kraepelin E. Dementia Praecox and Paraphrenia. Barclay RM, trans. New York: Krieger Publishing Company; 1971.
19. Hays P. The nosological status of schizophrenia. Lancet 1984;1:1342–5.

Peter Hays, FRCPC
Sooke, British Columbia

Neuroleptic Malignant Syndrome Due to Citalopram Overdose

Dear Editor:

Pathogenesis of the neuroleptic malignant syndrome (NMS) is not fully known. Several agents have been mentioned, but no citalopram-induced case has been reported. We report the first case of NMS due to citalopram.

Case Report

A 20-year-old man with no psychiatric or medication history attempted suicide by ingesting 1900 mg of citalopram. Within 3 hours he became comatose and was brought to hospital. On admission, he was unconscious, corneal reflexes were lost, and breathing was spontaneous. He developed subfebrile fever (37.5°C) and mild rigidity of the limbs, neck, and abdominal muscles. His pulse was 90 bpm, and his blood pressure was 90/60 mm Hg. He was given oxygen and mannitol (500 ml intravenously). After 2 days, swelling was seen on his chest, and crepitations were palpated. Due to spontaneous pneumothorax, the patient was intubated, and a chest drainage tube and right subclavian catheter were inserted. Lung radiogram was normal, and mechanical ventilation was instituted. After 6 days, the patient was extubated, and oxygen was given by mask; he tolerated the mask, but he was still unconscious, and his rigidity increased. On day 7, serum creatine kinase was found to be increased (1258 U/l) and NMS was suspected. The patient was started on bromocriptine 7.5 mg daily. After 6 hours, the patient began to regain consciousness, with intermittent agitation. With bromocriptine treatment, the level of consciousness returned to normal within 24 hours, and all symptoms disappeared. On day 10, medication was stopped, and the patient was discharged.

Citalopram is a potent inhibitor of the reuptake of serotonin in nerve endings. It has been reported that at doses below 600 mg daily mild symptoms such as nausea, dizziness, tachycardia, tremor, drowsiness, and somnolence can be observed. Doses of 600 mg to 1.9 g cause convulsions in patients, and the frequency increases at doses of 1.9 g to 5.2 g. Single cases of rhabdomyolysis, hypokalemia, and aspiration pneumonia have also been reported (1).

NMS results primarily from an imbalance of central neurotransmitters,

usually due to neuroleptic drug use; it is characterized by hyperthermia, muscular rigidity, and altered consciousness. Butyrophenones, phenothiazines, thioxanthenes, and dibenzoxazepines are believed to act as dopamine receptor-blocking agents. Atypical antipsychotics and fluoxetine, as well as dopamine blockers used to treat gastrointestinal disease, have also caused the syndrome (2). Although classically only neuroleptics have been considered to induce NMS (3), it has also been reported regularly with the use of other drugs that alter dopaminergic function, both with the cessation of dopamine agonists and with the administration of trycyclic antidepressants as well as monoamine oxidase inhibitors. NMS has also been associated with amoxapine use (4).

To date, no case report has been introduced in the literature related to citalopram-induced NMS, and this case is therefore the first report in the literature. Although this case did not meet all the criteria of NMS, the response to bromocriptine treatment was excellent.

Serotonin inhibitors may increase central serotonin levels, which may lead to an imbalance of the ratio of dopamine to serotonin. This may cause a relative central hypodopaminergic state (5). Therefore, in the present case, NMS may have occurred as a result of relative dopaminergic decrease due to citalopram overdose.

Finally, NMS etiology and criteria need to be reviewed, and it should be taken into consideration that selective serotonin reuptake inhibitors may induce NMS.

References

1. Personne M, Persson H, Sjöberg G. Citalopram toxicity. Lancet 1997;16:518–9.
2. Rippe JM, Irwin RS, Fink MP, Cerra FB. Disorders of temperature control: hyperthermia. In: Curley FJ and Irwin RS, editors. Intensive Care Medicine. Volume 1. Boston: Brown and Company; 1996. p 859–74.
3. Jaine KK. Neuroleptic malignant syndrome. In: Jain KK, editor. Drug-induced neurological disorders. Seattle: Hogrefe and Huber; 1996.
4. Assion HJ, Heinemann F, Laux G. Neuroleptic malignant syndrome under treatment with antidepressants? A critical review. Eur Arch Psychiatry Clin Neurosci 1998;248:231–9.
5. Halman M, Goldbloom DS. Fluoxetine and neuroleptic malignant syndrome. Biol Psychiatry 1990;28:518–21.

Nazan Aydin, MD
Enol Anaç, MD
Ali Çayköylü, MD
Fatih Akçay, MD
Erzurum, Turkey