Catatonia 20 Years Later

TO THE EDITOR: Gjessing and Gjessing (1) described periodic catatonia as a syndrome of reappearing excitement or stupor. Gjessing (2) and Annel (3) reported that lithium carbonate was successful in extending the period between episodes of periodic catatonia. Two reports have described cases of periodic catatonia that responded to lithium carbonate (4, 5). We present the case of a patient with long-standing periodic catatonia who was successfully treated with lithium carbonate.

Ms. A was a 55-year-old woman who upon admission reported having experienced bizarre and paranoid behavior, disorientation, amnesia, and reduced responsiveness over the previous month. She was in a deeply stuporous state and was diagnosed with schizophrenia. Her course in the hospital was characterized by episodes of greater motor activity, which would alternate with stuporous periods that would last several days. Results of a physical examination, computerized tomography scan, and an EEG revealed no abnormality. Her symptoms resolved after six ECT treatments.

Ms. A had had 14 admissions over 13 years that had been similar in presentation. Results of physical examinations and investigations that included thyroid function tests repeatedly showed no abnormality. A regimen of sodium amytal, 450 mg i.v., resulted in temporary symptomatic improvement but did not elicit additional information. She continued to respond to ECT but did not respond to maintenance treatments of haloperidol, 4 mg t.i.d.; pimozide, 2 mg t.i.d.; loxapine, 37.5 mg/day; amitriptyline, 100 mg h.s.; tranylcypromine, 10 mg t.i.d.; or various benzodiazepines. All medication trials had been longer than 4 weeks' duration. She had developed cholestatic jaundice while on a regimen of thioridazine. Ms. A was treated with lithium carbonate, 300 mg t.i.d. Her catatonia resolved and has not recurred in 7 years.

The possibility that remission of symptoms was coincident with the natural resolution of the illness is unlikely, considering the protracted course, the remarkable response, and the subsequent prolonged remission. In retrospect, a trial of maintenance ECT could have been attempted, given the poor pharmacological responses.

Abrams and Taylor (6) demonstrated that catatonia exists in patients with schizophrenia, mood disorders, and organic disorders. A study by Benegal et al. (7) suggests that catatonia can exist independent of any known disorder. Fink (8) has argued for a separate diagnostic classification for catatonia.

The clinical presentation was not consistent with a typical mood disorder, and symptoms were resistant to neuroleptic treatment. Although this does not preclude catatonia due to schizophrenia, the cyclical nature of symptoms and response to lithium carbonate suggest catatonia due to an atypical mood disorder, or a separate idiopathic etiology.

REFERENCES

1. Gjessing R, Gjessing L: Some main trends in the clinical aspects of periodic catatonia. Acta Psychiatr Scand 1961; 37:1–13
2. Gjessing LR: Lithium citrate loading of a patient with periodic catatonia. Acta Psychiatr Scand 1967; 43:372–375
3. Annel AL: Lithium in the treatment of children and adolescents. Acta Psychiatr Scand Suppl 1976; 207:19–30
4. Petursson H: Lithium treatment of a patient with periodic catatonia. Acta Psychiatr Scand 1976; 54:248–253
5. Wald D, Lerner J: Lithium in the treatment of periodic catatonia: a case report. Am J Psychiatry 1978; 135:751–752
6. Abrams R, Taylor MA: Catatonia: a prospective clinical study. Arch Gen Psychiatry 1976; 33:579–581
7. Benegal V, Hingorani S, Khanna S: Idiopathic catatonia: validity of the concept. Psychopathology 1993; 26:41–46
8. Fink M: Is catatonia a primary indication for ECT? Convuls Ther 1990; 6:1–4

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Vitamin C for Paroxetine- and Fluvoxamine-Associated Bleeding

TO THE EDITOR: Paroxetine is a selective serotonin reuptake inhibitor (SSRI) that is widely used for treatment of depression, obsessive-compulsive disorder, and panic disorder. There have been several reports of bleeding abnormalities connected with the use of SSRIs (1–4). I report here the case of a patient with panic disorder who developed bleeding related to the use of paroxetine and fluvoxamine.

Ms. A was a 33-year-old woman who had been suffering from panic disorder with agoraphobia for 2 years. Panic symptoms had begun after her father died. At that time she was also under considerable stress because of marital problems. At first she was successfully treated with a regimen of clomipramine, 100 mg/day. Because of persistent side effects, her medication regimen was changed to paroxetine, 40 mg/day. She was also being treated as necessary with lorazepam (1 mg) and temazepam (10 mg). The medication was well tolerated, and within months the symptoms had subsided. However, she complained of subjective agitation, a side effect that is quite commonly seen with paroxetine. Two weeks after she had started paroxetine treatment, she mentioned spontaneous bruising on her arms and legs and excessive menstrual blood loss, but she did not connect these with the medication. She had never had these complaints before. Gynecological examination did not reveal any abnormalities. Prothrombin time was 18 seconds (reference value: <24), and partial thromboplastin time was 41 seconds (reference value: <40). Results of other hematological laboratory tests were normal, and she was in good health. It did not seem that the marginal increase in the prothrombin time was a satisfactory explanation for her tendency to bleed, especially since there have been no reports in the literature about a relation between SSRI-associated bleeding and abnormalities of blood coagulation. Ms. A was given 500 mg/day of vitamin C; this caused the bleeding to stop within 3 weeks. Subsequently, she was asked to stop the vitamin C, which led to a gradual recurrence of ecchymosis and excessive menstrual blood loss. Shortly afterward the paroxetine regimen had to be discontinued because of her subjective feeling of agitation; she was then given fluvoxamine, 150 mg/day. The agitation ceased, as did the bleeding. However, the bleeding soon began again, and Ms. A was advised to resume taking vitamin C; once again the bleeding stopped.

The idea for using vitamin C was based on the knowledge that long ago citrus fruit was used in the Dutch navy to reduce the bleeding in sailors who had scurvy. There is one case report in the Dutch medical literature in which the use of vitamin C stopped bleeding related to SSRI medication (5). The main

mechanism underlying bleeding in scurvy is probably greater fragility of the capillaries. I believe that this case report shows that bleeding is a side effect of SSRI medication, as reported in the literature. I suggest that an increase in capillary fragility might be an explanation and that vitamin C could be used as therapy.

REFERENCES

1. Aranth J, Lindberg C: Bleeding, a side effect of fluoxetine (letter). Am J Psychiatry 1992; 149:412
2. Gunzberger DW, Martinez D: Adverse vascular effects associated with fluoxetine (letter). Am J Psychiatry 1992; 149:1751
3. Ottervanger JP, Stricker BHC, Huls J, Weeda JN: Bleeding attributed to the intake of paroxetine (letter). Am J Psychiatry 1994; 151:781–782
4. Calhoun JW, Calhoun DD: Prolonged bleeding time in a patient treated with sertaline (letter). Am J Psychiatry 1996; 153:443
5. Rasker MC: Bloedingsrisico bij gebruik van fluoxetine of fluvoxamine (letter). Ned Tijdschr Geneesk 1993; 137:618

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Cyproheptadine: A Potent In Vivo Serotonin Antagonist

TO THE EDITOR: Clozapine, the prototypical atypical antipsychotic, exhibits higher serotonin (5-HT_2) than dopamine (D_2) blockade in vivo, while typical neuroleptics block mainly D_2 receptors. It has been suggested that this higher affinity for 5-HT_2 receptors contributes to clozapine's greater efficacy and lower propensity for extrapyramidal side effects (1, 2). Several new antipsychotics (e.g., olanzapine, sertindole, seroquel) are being tested because of their higher 5-HT_2 than D_2 affinity, and one (risperidone) has already been introduced. High 5-HT_2 blockade and modest D_2 blockade can also be obtained with the use of two medications: sufficient amounts of one with prominent 5-HT_2 antagonism and relatively lesser amounts of another with D_2 antagonism. This latter approach offers the possibility of individualized and flexible titration of the 5-HT_2/D_2 antagonism to obtain optimal effects in a given individual. While there are several D_2 antagonists available, there are no well-characterized 5-HT_2 antagonists for regular human use. Cyproheptadine, a safe and widely available antiallergy/appetite-stimulant medication, is known to block 5-HT_2 receptors in vitro with high (1–3 nM) affinity. We describe the first in vivo study to report the 5-HT_2 profile of cyproheptadine in humans through the use of [18F]-setoperone positron emission tomography (PET) scans.

Two normal volunteers (a 31-year-old man and a 27-year-old man) participated after providing written informed consent as per procedures approved by the University of Toronto Committee on the Use of Human Subjects. Both subjects had their 5-HT_2 receptors assessed twice: before and 4 hours after the last dose of cyproheptadine (4 mg t.i.d. and 6 mg t.i.d., respectively, for 6 days each). [18F]-setoperone PET scans were done 4 hours after the last morning dose in accordance with published procedures (3). The prefrontal cortex has a high density of 5-HT_2 receptors, while the cerebellum is essentially devoid of them. The specific prefrontal uptake (i.e., prefrontal minus cerebellar) of [18F]-setoperone can be completely displaced by a specific 5-HT_2 antagonist such as ketanserin, while the cerebellar uptake is unaffected (3). Therefore, the steady state (65–90 minutes after the injection) prefrontal/cerebellum ratio, which reflects the B_{max}/K_d for the 5-HT_2 receptors, can be used as an index of available 5-HT_2 receptors. We have standardized this procedure in our laboratory with high scan-rescan and interrater reliability (intraclass correlation coefficients of 0.94 and 0.95, respectively). The prefrontal regions of interest were drawn on the pretreatment scan and were transferred to the posttreatment scan. At 4 mg t.i.d., cyproheptadine blocked 85% of the available 5-HT_2 receptors in the prefrontal cortex, and at 6 mg t.i.d. it blocked over 95%.

These PET findings demonstrate that at its usual clinical dose (12–18 mg/day), cyproheptadine is a potent in vivo 5-HT_2 antagonist. This finding has important implications for the therapeutics in schizophrenia. In a recent review (2), we proposed that optimal benefit of 5-HT_2/D_2 antagonism is obtained when 1) the in vivo 5-HT_2 occupancy is higher than the D_2 occupancy, and 2) the D_2 receptor system is not greater than 80%. Our present finding suggests that it may be possible to combine cyproheptadine (4–6 mg t.i.d.) with a low dose of a typical neuroleptic (D_2 antagonist) to obtain the optimal 5-HT_2/D_2 combination. In testing this approach it will be critical to hold the levels of D_2 blockade at modest levels, since the potential benefit of 5-HT_2 blockade may be lost if the D_2 blockade is too high (2, 4). In this regard we would be happy to share data regarding the relationship between dose and D_2 blockade for typical neuroleptics with colleagues who are interested in testing such combinations clinically. If such a combination strategy is successful, it opens the possibility of optimal titration of the 5-HT_2/D_2 occupancy in individual patients in an effort to maximize treatment benefits.

REFERENCES

1. Meltzer HY, Matsubara S, Lee JC: The ratios of serotonin-2 and dopamine-2 affinities differentiate atypical and typical antipsychotic drugs. Psychopharmacol Bull 1989; 25:390–392
2. Kapur S, Remington G: Serotonin-dopamine interaction and its relevance to schizophrenia. Am J Psychiatry 1996; 153:466–476
3. Blin J, Sette G, Fiorelli M, Bletry O, Elghozi JL, Crouzel C, Baron JC: A method for the in vivo investigation of the serotonergic 5-HT2 receptors in the human cerebral cortex using positron emission tomography and 18F-labeled setoperone. J Neurochem 1990; 54:1744–1754
4. Kapur S, Remington G, Zipursky RB, Wilson AA, Houle S: The D2 dopamine receptor occupancy of risperidone and its relationship to extrapyramidal symptoms: a PET study. Life Sci 1995; 57:PL103–PL107

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Telemedicine in Psychiatry: Making the Dream Reality

TO THE EDITOR: Because our clinical decisions are based on data from face-to-face interviews, which can be well conveyed by inexpensive, medium bandwidth digital linkages, telemedicine has particular applicability to psychiatry (1, 2). However, in the current climate of managed care, it is critical to use telepsychiatry strategically to enhance the quality of care while controlling the cost of its delivery. For this reason, we focused on the use of telemedicine in emergency evaluations of acutely ill psychiatric patients who require such assessment for admission or involuntary commitment to an inpatient unit.