## Clozapine-Induced Stuttering and Seizures

TO THE EDITOR: Stuttering induced by psychotropic agents has been anecdotally described as being associated with clozapine treatment (1–3). We describe an instance of clozapine-induced stuttering in a patient who later developed generalized seizures.

**Mr. A, a 28-year-old man who had been diagnosed with paranoid schizophrenia of 8 years' duration, was treated with clozapine because treatment resistance. An EEG performed when he was receiving 150 mg/day of clozapine showed bilateral frontotemporal slowing (left more than right), generalized nonparoxysmal sharp and slow waves, and a photic convulsive response. Because Mr. A was having a good response to clozapine, it was decided to continue giving him clozapine under close supervision. However, at a clozapine dose of 300 mg/day, he developed stuttering, which worsened with further increases.**

**At that point, we were unaware of any association between clozapine and stuttering. It was only when Mr. A developed severe stuttering and subsequently had a generalized tonic-clonic seizure when he was taking 425 mg/day of clozapine that we considered that the stuttering might be related to clozapine-induced seizures. We then performed a literature search on PubMed using the key words "clozapine" and "stuttering," which yielded three related reports (1–3). Our observation of clozapine-induced stuttering was supported by the dramatic improvement in Mr. A's stuttering after his clozapine dose was reduced to 200 mg/day. Concurrently, we started treatment with valproate and titrated the dose up to 800 mg/day.**

**An EEG taken a day after Mr. A's generalized seizure showed generalized nonparoxysmal slowing and a photic convulsive response in posterior regions of the brain. The association between stuttering and seizures was further bolstered by the fact that Mr. A did not have a reemergence of stuttering when his dose of clozapine was again increased to 300 mg/day (the dose at which stuttering had initially appeared) while he was also taking valproate. A normal EEG corroborated this evidence.**

This report supplements the only report that we know of that relates clozapine-induced stuttering to epileptic brain activity (3). An association between stuttering and dystonia has been previously described (1), but our patient showed no evidence of dystonia, which was thus excluded as a cause of stuttering. The authors of that report (1) may have misattributed stuttering to coincidental dystonia, although their patient had significant EEG abnormalities.

Stuttering has been demonstrated to occur in association with seizures and to respond to treatment with antiepileptic drugs (4). Patients with stuttering without seizures have also been shown to have EEG abnormalities, such as background activity that is too slow for age (5). When coupling this observation with the hypothesis that patients with stuttering may have predominantly left-sided abnormality (6), it is tempting to speculate, albeit with caution, that stuttering accompanied by EEG abnormalities—especially left-sided slowing (as in this case)—in patients taking clozapine may be a harbinger of seizures. Further studies are required to address this issue.


**References**

1. Thomas P, Lalaux N, Vaiva G, Goudemand M: Dose-dependent stuttering and dystonia in a patient taking clozapine (letter). Am J Psychiatry 1994; 151:1096
2. Ebeling TA, Compton AD, Albright DW: Clozapine-induced stuttering (letter). Am J Psychiatry 1997; 154:1473
3. Supprian T, Retz W, Deckert J: Clozapine-induced stuttering: epileptic brain activity? (letter). Am J Psychiatry 1999; 156:1663–1664
4. Nowack WJ: Adult onset stuttering and seizures. Clin Electroencephalogr 1986; 17:142–145
5. Klepel H, Kuhne GE, Mackerodt G: [Incidence of electroencephalographic findings in children with stuttering compared to healthy children of the same age]. Psychiatr Neurol Med Psychol (Leipz) 1982; 34:488–492 (German)
6. Geschwind N, Galaburda AM: Cerebral lateralization: biological mechanisms, associations, and pathology, I: a hypothesis and a program for research. Arch Neurol 1985; 42:428–459



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## Transcranial Magnetic Stimulation for Panic

TO THE EDITOR: Studies have suggested that fast repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex is a promising treatment strategy for major depression (1). Moreover, slow rTMS of the right dorsolateral prefrontal cortex has been also shown to improve symptoms of depression and posttraumatic stress disorder (2). However, studies of its anxiolytic properties are hampered by the complex symptom profile of the anxiety disorders. Thus, the investigation of rTMS in a specific paradigm of experimentally induced anxiety theoretically may be a promising avenue for testing whether rTMS exerts specific anxiolytic effects.

The administration of cholecystokinin tetrapeptide (CCK-4) provokes panic-like symptoms both in healthy volunteers and in patients with panic disorder that can be blocked by use of antipanic agents, such as benzodiazepines and antidepressants (3), and may therefore serve to test the anxiolytic properties of new therapeutic strategies. We report on a patient treated with right prefrontal rTMS who showed a reduction in panic disorder symptoms and improvement in CCK-4–induced panic attacks, associated with blunting of the CCK-4–induced elevation of ACTH and cortisol.

**Ms. A, a 52-year-old woman, had been suffering from panic disorder (according to DSM-IV criteria) with six panic attacks per week for 13 months. She had not received any prior treatment and was medication free at the time of admission. Ms. A gave her informed consent for treatment after the procedure had fully been explained to her; she was treated in a pilot investigation with slow rTMS of the right dorsolateral prefrontal cortex for 2 weeks (10 sessions, 1200 stimuli/day, 1 Hz, 110% intensity, which was related to individual motor threshold). At baseline and after rTMS treatment, a CCK-4 challenge was performed to assess the putative effects of rTMS in its ability to induce panic attacks. Panic symptoms were assessed by applying the Acute Panic Inventory (4) and the Panic Symptom Scale (5). Cortisol and ACTH plasma levels were determined during the challenge. Ratings for general anxiety**

**and naturally occurring panic attacks were assigned after use of the Hamilton Anxiety Rating Scale and Bandelow's Panic and Agoraphobia Scale (6).**

**After 2 weeks of rTMS, Ms. A reported a marked improvement in her anxiety. Her score on the Hamilton anxiety scale had decreased from 27 to 6 (–78%), and her score on the Panic and Agoraphobia Scale had decreased from 34 to 14 (–59%). Moreover, a marked reduction in her CCK-4–associated panic symptoms was observed after the second challenge. Her maximum scores on the Acute Panic Inventory and the Panic Symptom Scale decreased from 34 to 20 (–41%) and from 38 to 26 (–32%), respectively. Her maximum serum cortisol level CCK-4 challenge decreased from 884 nmol/liter to 0 nmol/liter; her maximum serum ACTH level decreased from 1.47 pmol/liter to 0.35 pmol/liter. At her 4-week follow-up examination, Ms. A's condition was stable, so she did not require further pharmacotherapy.**

This report adds to previous evidence that slow rTMS of the right prefrontal cortex ameliorates the symptoms of major depression and anxiety disorders (1). In contrast, single instances of panic disorder and generalized anxiety disorder have been reported in which panic and anxiety increased after fast rTMS over left or right prefrontal sites (7). However, slow rTMS is hypothesized to be associated with the opposite effect on cortical excitability—namely, putative inhibitory net effects—in contrast to the augmentative effects of fast rTMS (8).

The clinical findings in the present case report are strengthened by the observation of a complete blunting of CCK-4–induced serum cortisol increase after rTMS, despite the occurrence of mild symptoms of anxiety. This is compatible with the putative effect of rTMS on hypothalamic-pituitary-adrenal reactivity to CCK-4 administration. However, in view of the high susceptibility of patients with panic disorder to placebo effects, we must consider the possibility that placebo effects may also have influenced our findings. Future studies should investigate the anxiolytic potential of rTMS in patients with panic disorder under placebo-controlled conditions.

### References


1. George MS, Lisanby SH, Sackeim HA: Transcranial magnetic stimulation: applications in neuropsychiatry. Arch Gen Psychiatry 1999; 56:300–311
2. McCann UD, Kimbrell TA, Morgan CM, Anderson T, Geraci M, Benson BE, Wassermann EM, Willis MW, Post RM: Repetitive transcranial magnetic stimulation for posttraumatic stress disorder. Arch Gen Psychiatry 1998; 55:276–279
3. Bradwejn J, Koszycki D: Imipramine antagonism of the panicogenic effects of cholecystokinin tetrapeptide in panic disorder patients. Am J Psychiatry 1994; 151:261–263
4. Dillon DJ, Gorman JM, Liebowitz MR, Fyer AJ, Klein DF: Measurement of lactate-induced panic and anxiety. Psychiatry Res 1987; 20:97–105
5. Bradwejn J, Koszycki D, Annable L, Couetoux du Tertre A, Reines S, Karkanias C: A dose-ranging study of the behavioral and cardiovascular effects of CCK-tetrapeptide in panic disorder. Biol Psychiatry 1992; 32:903–912
6. Bandelow B: Assessing the efficacy of treatments for panic disorder and agoraphobia, II: The Panic and Agoraphobia Scale. Int Clin Psychopharmacol 1995; 10:73–81
7. Greenberg BD, McCann U, Benjamin J, Murphy DL: Repetitive TMS as a probe in anxiety disorders: theoretical considerations and case reports. CNS Spectrums 1997; 2:47–52
8. Speer AM, Kimbrell TA, Wassermann EM, Repella D, Willis MW, Herscovitch P, Post RM: Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. Biol Psychiatry 2000; 48:1133–1141



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## Nortriptyline for Depression and Vulvodynia

TO THE EDITOR: There is an intimate and complex relationship between depression and pain, and patients suffering from depression are at a greater risk for developing various chronic pain syndromes than individuals without depression (1). Vulvodynia, a neuropathic pain syndrome that affects the vulva and external genitalia, is often associated with depression (2, 3). It has been suggested that the condition may respond favorably to antidepressant treatment (2), but to date we are aware of no specific case reports, much less controlled studies, on the topic. We recently cared for a patient with major depression and vulvodynia who responded dramatically to treatment with a tricyclic antidepressant.

**Ms. A, a 78-year-old woman, had developed prolonged major depression after a herpes zoster infection. The infection had involved the left T10 or T11 dermatome and had remitted with no residual post-therapeutic neuralgia; her depression had responded partially to trials of 40 mg/day of paroxetine, 225 mg/day of venlafaxine, 15 mg/day of mirtazapine, and 20 mg/day of citalopram. She had no past psychiatric history, and her past medical history was positive only for hypertension. During the same time that the depression developed, she began to complain of a severe burning sensation around her vaginal introitus with no clear exacerbating or relieving factors. She was not sexually active, and there was no history of sexual trauma. A pelvic examination was remarkable only for atrophic vaginitis; there was minimal to no inflammation and no discharge.**

**Over the subsequent 2 years, Ms. A was treated empirically with estrogen cream, as well as a variety of topical and vaginal antifungal creams, topical hydrocortisone cream, and, ultimately, viscous lidocaine and oral codeine. Neither these treatments nor the antidepressants proved effective for pain control. Ultimately, it was decided to change her antidepressant to a tricyclic agent to improve the vaginal pain as well as the depression. Ms. A began taking nortriptyline, 25 mg at bedtime, which yielded a serum level of 92 ng/ml. Nortriptyline proved quite effective for her depression and, fortuitously, also resulted in complete resolution of the vaginal pain.**

To our knowledge, there has been only a single positive open trial of antidepressants for chronic pelvic pain (4), but vulvodynia is felt to be a distinct syndrome (3). Its dysesthetic character, lack of associated tissue pathology, and strong association with depression are reminiscent of other neuropathic syndromes, such as facial neuralgia and glossodynia. Our patient responded dramatically to treatment with a tricyclic antidepressant but not to a variety of other agents. (Spontaneous remission is a possibility but seems unlikely after 2 years of unremitting symptoms.) It is unclear whether this

was because of her better response to nortriptyline or to the inherent superior efficacy of tricyclics in the treatment of neuropathic pain (5). Further studies will be necessary to establish the efficacy of antidepressants in general, and tricyclics in particular, in the treatment of vulvodynia.

### References


1. Von Korff M, LeResche L, Dworkin SF: First onset of common pain symptoms: a prospective study of depression as a risk factor. Pain 1993; 55:251–258
2. Ridley CM: Vulvodynia: theory and management. Dermatol Clin 1998; 16:775–778, xiii
3. Bodden-Heidrich R, Kuppers V, Beckmann MW, Ozornek MH, Rechenberger I, Bender HG: Psychosomatic aspects of vulvodynia: comparison with the chronic pelvic pain syndrome. J Reprod Med 1999; 44:411–416
4. Walker EA, Roy-Byrne PP, Katon WJ, Jemelka R: An open trial of nortriptyline in women with chronic pelvic pain. Int J Psychiatry Med 1991; 21:245–252
5. Lynch ME: Antidepressants as analgesics: a review of randomized controlled trials. J Psychiatry Neurosci 2001; 26:30–36


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## Clozapine for First-Episode Schizophrenia

TO THE EDITOR: The use of clozapine to treat first episodes of psychosis has rarely been reported (1, 2). We present the case of a young man with a first episode of schizophrenia who had a sustained, complete resolution of symptoms with clozapine treatment.

**Mr. A was a 30-year-old man who came to the emergency room after attempting suicide by overdose. In the preceding 6 months, he had noticed feelings of being watched and feared a Mafia plot against him. He had delusions of reference about the television and thought that strangers knew his history. He claimed to have telepathy, thought that energy was passing between people, and heard voices telling him to kill himself. The emergency room physician proposed a diagnosis of paranoid schizophrenia, which was confirmed when measured against DSM-IV criteria upon his first hospital admission by a physician experienced in schizophrenia research.**

**Six months earlier, Mr. A had been treated for depressive symptoms by a general practitioner, who prescribed an 8-week trial of paroxetine. Mr. A's family history had revealed alcoholism, depression, bipolar affective disorder, and suicide by an uncle. Mr. A reported drinking two to three beers per week and occasionally using cannabis.**

**When Mr. A was admitted for treatment of his first episode of psychosis, he initially had a short (2-week) trial of olanzapine. While he was still experiencing his first episode of psychotic illness, he consented to participate in the International Suicide Prevention Trial (InterSePT) and was given clozapine during a 4-week crossover period in which he received both antipsychotics. Clozapine, 12.5 mg/day, was gradually increased over 5 weeks to 100 mg/day and was maintained at a dose of 112.5 mg/day. Concomitant medication included only gabapentin, 2400 mg/day, for situational anxiety (3).**

**Mr. A's baseline scores were rated with the Positive and Negative Syndrome Scale (4) (positive symptoms: score=19, negative symptoms: score=20, total score=90), the Clinical Global Impression (CGI) scale (score=4), the Calgary Depression Scale (5) (depression: score=15, anxiety: score=5), the InterSePT Suicidality Scale (6) (score=9), and the Extrapyramidal Symptom Rating Scale (7) (parkinsonism: score=7, dyskinesia: score=1). After 8 weeks of treatment he had improved dramatically. He maintained this improvement, and after 2 years his total score on the Positive and Negative Syndrome Scale was 30 (minimal score=30), his CGI scale score was 1, his scores on the Calgary Depression Scale were 0 for both depression and anxiety, his InterSePT Suicidality Scale score was 0, and his score on the Extrapyramidal Symptom Rating Scale showed no movement disorder. After 2½ years of clozapine treatment, he lives with a roommate and works full-time in the aviation industry.**

Several authors have questioned whether clozapine should be indicated as a first-line treatment for early psychosis (1, 2, 8). The risk-benefit ratio has been reappraised (9) in view of the lower rates of relapse, hospitalization, extrapyramidal symptoms, and suicidality and the improvements in negative symptoms, cognition, and social functioning associated with clozapine. Long-term outcome studies of patients treated with clozapine early in the course of their illness and spared the neurotoxicity of long-term exposure to traditional antipsychotics are needed.

### References


1. Szymanski S, Masiar S, Mayerhoff D, Loebel A, Geisler S, Pollack S, Kane J, Lieberman J: Clozapine response in treatment-refractory first-episode schizophrenia. Biol Psychiatry 1994; 35:278–280
2. Hector RI: The use of clozapine in the treatment of aggressive schizophrenia. Can J Psychiatry 1998; 43:466–472
3. Chouinard G, Beauclair L, Belanger MC: Gabapentin: long-term antianxiety and hypnotic effects in psychiatric patients with comorbid anxiety-related disorders (letter). Can J Psychiatry 1998; 43:305
4. Kay SR, Fiszbein A, Opler LA: The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13:261–276
5. Addington D, Addington J, Maticka-Tyndale E, Joyce J: Reliability and validity of a depression rating scale for schizophrenics. Schizophr Res 1992; 6:201–208
6. Lindenmayer JP, Czobor P, Alphs A, Anand R, Islam Z, Pestreich L: The InterSePT Scale for Suicidal Thinking (ISST): A new assessment instrument for suicidal patients with schizophrenia (abstract). Schizophr Res 2001; 49(suppl 1–2):5
7. Chouinard G, Ross-Chouinard A, Annable L, Jones B: The Extrapyramidal Symptom Rating Scale (abstract). Can J Neurol Sci 1980, 7:233
8. Green AI, Schildkraut JJ: Should clozapine be a first-line treatment for schizophrenia? the rationale for a double-blind clinical trial in first-episode patients. Harv Rev Psychiatry 1995; 3: 1–9
9. Meltzer HY, Okayli G: Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. Am J Psychiatry 1995; 152:183–190


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## Mania in Hyperandrogenism, Insulin Resistance, and Nigricans Acanthosis Syndrome

TO THE EDITOR: Hyperandrogenism, insulin resistance, and acanthosis nigricans (HAIR-AN) syndrome has been defined only in the past 20 years and may be present in as many as 1%–3% of all women with hyperandrogenism (1). A case of organic mood disorder (depressed type) associated with the HAIR-AN syndrome, which improved markedly in response to ovarian suppression with oral contraceptives, has been documented (2). In this report, we describe a patient with HAIR-AN syndrome who developed her first manic episode after she had stopped taking her birth control pills 2 months earlier.

**Ms. A, a 19-year-old Hispanic woman with no prior psychiatric diagnosis, was brought to the emergency department by police during a manic episode. When she arrived at the medical center, her symptoms were characterized by an elevated mood, a lessened need for sleep, racing thoughts, and pressured speech. She also exhibited grandiose delusions, believing that she was the messenger of God and that she was so rich that she could buy 50 cars for the poor. At further questioning, Ms. A indicated that she had run away from home a week before admission, after a disagreement with her stepfather.**

**Her past medical history revealed a history of hirsutism and a diagnosis of polycystic ovary disease. Ms. A had been treated with oral contraceptives for about 6 months. She had stopped taking the birth control pills 2 months before the current episode. Although Ms. A reported a history of marijuana and cocaine abuse, her urine and serum toxicology screens at admission were negative for any substance. The results of other routine laboratory tests, including a CBC and measurements of glucose, blood urea nitrogen, creatinine, potassium, sodium, chloride, bicarbonate, and thyroid-stimulating hormone, were within normal limits.**

**Ms. A's physical examination was significant for a male pattern of hair growth on her face and hyperpigmented skin on the nape of her neck. The results of subsequent endocrinological tests were consistent with the diagnosis of HAIR-AN syndrome: an elevated insulin level of 54.7 μU/ml (normal range=0–25 μU/ml), an elevated testosterone level of 0.93 ng/ml (normal range=0.14–0.76 ng/ml), a normal level of follicle-stimulating hormone (3.2 mIU/ml), and a normal level of luteinizing hormone (8.10 mIU/ml). The results of imaging studies, including magnetic resonance imaging of the head and an abdominal computerized tomography scan, were unremarkable and were not suggestive of growth in the pituitary or adrenal glands.**

**While she was in the hospital, Ms. A's manic symptoms were successfully treated with a combination of lithium, divalproex sodium, and quetiapine. She refused to take oral contraceptives, despite the possible association of her mood symptoms with the discontinuation of birth control pills. After 2 weeks of hospitalization, she returned home with her parents.**

The primary abnormality seen in patients with the HAIR-AN syndrome is believed to be insulin resistance with compensatory higher circulating insulin levels (1). Chronic elevated insulin is hypothesized to stimulate receptors for ovarian and epidermal insulin-like growth factors, resulting in hyperandrogenemia and hyperpigmentation, respectively (1, 3). Levin et al. (2) described a case of organic mood disorder (depressed type) in association with the HAIR-AN syndrome and noted that the patient's depressive symptoms improved with the initiation of oral contraceptives. However, no reported cases of mania associated with HAIR-AN syndrome have been described, to our knowledge. This report may represent the first documented case of mania in a patient with HAIR-AN syndrome; of more interest, the patient's manic symptoms emerged 2 months after she stopped treatment with oral contraceptives. However, we cannot overlook the possibility that our patient's manic episode was coincidental (in the context of HAIR-AN syndrome and the cessation of treatment with oral contraceptives) but find the association noteworthy and in need of further study.

### References

1. Barbieri RL, Ryan KJ: Hyperandrogenism, insulin resistance, and acanthosis nigricans syndrome: a common endocrinopathy with distinct pathophysiologic features. Am J Obstet Gynecol 1983; 147:90–101
2. Levin TR, Terrell TR, Stoudemire A: Organic mood disorder associated with the HAIR-AN syndrome. J Neuropsychiatry Clin Neurosci 1992; 4:51–54
3. Zemtsov A, Wilson L: Successful treatment of hirsutism in HAIR-AN syndrome using flutamide, spironolactone, and birth control therapy. Arch Dermatol 1997; 133:431–433

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## Suicide Attempt After Use of Herbal Diet Pill

TO THE EDITOR: Ma-huang, or ephedra, an extract of the plant species *Ephedra sinica,* grows mainly in Mongolia near the Chinese border. Its main compounds are alkaloids of the 2-aminophenylpropane type, *l*-ephedrine and *d*-pseudoephedrine (1), and it is found in many over-the-counter weight-loss aids. There have been reports (2–5) of significant adverse health consequences associated with its use. We report a case of suicide attempt and organically induced mood disorder associated with use of a diet pill containing Ma-huang.

**Ms. A, a 32-year-old mother of two children, was brought to the hospital in a comatose state after she had swallowed 80 tablets of acetaminophen, 60 tablets of an herbal weight-loss supplement, and an unknown number of multivitamin tablets. She had no past history of mood disorders, according to both herself and her husband. She had started using the herbal weight-loss supplement about 2 months before her hospitalization. She reported that since that time, she had been feeling depressed most of the time, had been irritable, and had poor impulse control at work and at home. She had yelled at her boss and at her husband and daughter and had thrown things at them during moments of rage. She also reported frequent suicidal ideation and feelings of guilt. She had more energy and slept less—no more than 3 hours a night. She also heard voices calling her name.**

**After the overdose, Ms. A was admitted into the intensive care unit, where supportive measures were administered. Her serum acetaminophen level was 182.31 μg/ml at admission and decreased to <1.00 μg/ml 2 days later. Her level of aspartate transaminase went from 239 U/liter at admission to 872 U/liter the next day, then down to 26**

**U/liter a week later. Her alanine transaminase level went up from 243 U/liter at admission to 971 U/liter the next day, then decreased to 530 U/liter a week later. Her LDH level was 1452 U/liter at admission.**

**After Ms. A regained consciousness, the results of a psychiatric evaluation revealed a slightly overweight woman with pressured speech, flight of ideas, an irritable and annoyed mood, and auditory hallucinations. These symptoms gradually subsided over 5 days without the administration of psychotropic medication. At the 5-month follow-up, Ms. A was euthymic, with no suicidal ideation, and was taking no psychotropic medication.**

The product label for the herbal weight-loss supplement that the patient took states that a two-tablet serving contains 324 mg of Ma-huang extract, standardized for 20 mg of ephedrine alkaloids. The recommended dose is two tablets per day. Our patient said that she had been taking four tablets per day for 2 months. There are many reports in the literature about the adverse effects of Ma-huang, including mania (2, 6), psychosis (4), hypertension (3), tachycardia (3), and myocardial infarction. Many deaths reported to the Food and Drug Administration (FDA) have been attributed to this herbal substance (4). The users of products containing Ma-huang are increasing in number, owing in large part to the fact that it is an herbal, or "natural," drug and thus is perceived as being safe. Some individuals exceed the recommended dose when they are self-medicating, and this can contribute further to adverse effects. Unfortunately, there are not enough studies of the safety and efficacy of this herb. Until we establish some kind of reporting system that allows the FDA to keep track of adverse reactions to Ma-huang, there will be many unidentified adverse events. That makes questioning patients regarding the use of over-the-counter remedies essential.

### References


1. Greenberg SB: PDR for Herbal Medicines, 1st ed, 1998, pp 826–827
2. Capwell RR: Ephedrine-induced mania from an herbal diet supplement (letter). Am J Psychiatry 1995; 152:647
3. Crone CC, Wise TN: Use of herbal medicines among consultation-liaison populations. Psychosomatics 1998; 39:3–13
4. Jacobs KM, Hirsch KA: Psychiatric complications of Ma-huang. Psychosomatics 2000; 41:58–62
5. Pies R: Adverse neuropsychiatric reactions to herbal and over-the-counter "antidepressants." J Clin Psychiatry 2000; 61:815–820
6. Emmanuel NP, Jones C, Lydiard RB: Use of herbal products and symptoms of bipolar disorder (letter). Psychiatry 1998; 155: 1627


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## Use of Dreams by Psychopharmacologists

TO THE EDITOR: In a recent issue, Morton F. Reiser, M.D. (1), brought together sources from psychoanalysis and neuroscience to evaluate the role of the dream in current psychiatric thinking. I would like to add a contribution from psychopharmacology to the subject. Since the dream records first and foremost the current affect of the patient, it can—and, I believe, should—be used in the psychopharmacologic treatment of mental illness. Whether or not the dream is "the royal road to the unconscious"—and I believe it is—it is certainly the royal road to the affect. In my experience, the initial affect of the dream or sequence of dreams corresponds to the affect with which the patient awakens. I believe that the ultimate target symptom to be addressed in psychopharmacology is the patient's affect, and it is for this reason that the dream provides a quick and efficient source of information—or, rather, supplementation to other clinical data—for the purpose of deciding which medication to prescribe and how to modify the dose. A description of a recent patient illustrates this concept.

**Mr. A was a 24-year-old man with severe anorexia nervosa who had no improvement after 10 hospitalizations in programs for the treatment of eating disorders and the efforts of a number of psychopharmacologists. He had had many types of pharmacologic intervention, and when I first saw him, he was taking 40 mg/day of fluoxetine because his anorexia nervosa was complicated by severe obsessive-compulsive neurosis. However, I saw no depressive affect in Mr. A. On the contrary, the most recent dream he could recall was that he was in bed with a "very pretty girl." That did not sound like a depressive dream to me but, rather, a dream that indicated a euphoric mood. His appearance at consultation was also euphoric. There was no sexual activity in the dream; he had never experienced any sexual contact with a partner. However, he was very close to his mother, who was very sympathetic and indulgent, in contrast to his father, who was harsh and critical.**

**I reasoned that the anorexia nervosa might have been a self-destructive effort to counteract his "up" mood in the same way that self-defeating behavior on the part of patients with mania can be seen as a corrective attempt and often interpreted as punishment. Accordingly, I prescribed olanzapine, 10 mg/day, primarily as a depressive drug, although I was obviously taking advantage of its propensity for increasing Mr. A's appetite. Within 3 days, for the first time in years, Mr. A began eating eagerly and with appetite. I gradually increased his dose of olanzapine to 20 mg/day, wondering whether I might not be pressing too hard. However, Mr. A came in delighted with his change in status and reported his weight gain to me daily.**

**We had been discussing Mr. A's difficulty in finding appropriate women to date. One day he reported having a dream in which he was with two girls who told him that they heard him "farting," that he was "shitty," and that "they would not have anything to do" with him. He started to weep as he described the dream. Clearly, this was a change in affect and indicated a switch in mood to the depressive side, which I had anticipated. I reduced his dose of olanzapine to 15 mg/day and added 15/mg day of mirtazapine. He then recovered completely.**

Thus, the dream can be used advantageously by psychopharmacologists. However, from a theoretical point of view, we may infer also that the dream primarily expresses affect directly and probably selects content from the store of memories associated with that affect. What Freud called "dream work" creates a story line of sorts that integrates the images and processes of the dream. It does not do nearly as well as waking consciousness does, but it does integrate the affects, images, and processes admitted to our waking consciousness.

### Reference

1. Reiser MF: The dream in contemporary psychiatry. Am J Psychiatry 2001; 158:351–359



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## Antistreptolysin-O Titers: Implications for Adult PANDAS

TO THE EDITOR: A diagnosis of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is made when neuropsychiatric disease is precipitated by streptococcal infection (1). Antistreptolysin-O titers are an important tool for diagnosing recent streptococcal infection in patients with Sydenham's chorea and PANDAS, since throat cultures are usually negative because of the latent onset of the neuropsychiatric disease. The upper limit for normal antistreptolysin-O titers is 200 IU/ml in children, but no normal upper limit exists for healthy adults. We propose that an antistreptolysin-O titer of 270 IU/ml is the significant upper limit for healthy adults. This finding will aid in the investigation and diagnosis of new cases of adult PANDAS.

Because of recent reports of cases of PANDAS in adults (2, 3), we measured antistreptolysin-O titers for 50 healthy adults to determine a normal adult range and investigated the number of healthy adults with higher than normal antistreptolysin-O titers. Fifty healthy adults (25 men and 25 women) were recruited from the staff of a pediatric hospital between November 2000 and May 2001; they had a mean age of 35.6 years (range=19–57). Subjects were excluded if there was a history of neurological, psychiatric, or autoimmune disease. The time of their most recent sore throat was recorded; 30% of the subjects had had a sore throat within the 6 months before the blood sampling. Blood samples were processed within 1 day of receipt, and antistreptolysin-O titers were measured by using a standardized nephelometry technique.

The subjects' mean antistreptolysin-O titer was 122 IU/ml (range=50–376). Only 8% (four of 50) of the healthy adults had antistreptolysin-O titers higher than 200 IU/ml, 4% (two of 50) had titers over 300 IU/ml, and none had titers over 400 IU/ml. According to the upper limit of 200 IU/ml for a normal pediatric antistreptolysin-O titer, 8% (four of 50) of the healthy adults had "abnormal" titers. In this healthy adult group, the upper limit (95th percentile) for a normal antistreptolysin-O titer was 270 IU/ml.

The patients with recent cases of adult PANDAS both had highly elevated antistreptolysin-O titers of 1600 IU/ml (2) and 739 IU/ml (3). We conclude that streptococcal serology is a useful diagnostic tool for assessing the etiology of new cases of neuropsychiatric disease in adults and propose an antistreptolysin-O titer of 270 IU/ml as the upper limit of normal for adults.


### References

1. Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, Perlmutter S, Lougee L, Dow S, Zamkoff J, Dubbert BK: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am J Psychiatry 1998; 155:264–271; erratum, 155:578
2. Bodner SM, Morshed SA, Peterson BS: The question of PANDAS in adults. Biol Psychiatry 2001; 49:807–810
3. Mathew SJ: PANDAS variant and body dysmorphic disorder (letter). Am J Psychiatry 2001; 158:963



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## Pramipexole for Depression

TO THE EDITOR: Pramipexole is a dopamine agonist that is active primarily at the dopamine $D_3$ receptor but also at $D_2$ and to a lesser extent at $D_4$. It was introduced for the treatment of idiopathic parkinsonism.

I noticed the use of pramipexole for the treatment of depression in a note in *Psychiatry Drug Alerts*. Initial reports suggested the use of pramipexole as an augmentation for current treatment with antidepressants—later and more hesitantly it was suggested as primary therapy. I am aware of no systematic large-scale studies of pramipexole as a treatment for depression.

My small group included 22 patients, 11 of each gender, who were treated in the course of psychoanalytic psychotherapy. They ranged in age from 20 to 60 years. They received treatment from less than 1 month to more than 6 months. In eight instances, pramipexole was combined with other antidepressant medications. Twenty of these patients had depression with another diagnosis on the manic-depressive spectrum, including borderline personality disorder. Two patients were severely inhibited, with profoundly low self-esteem. Eight experienced rapid cycling. The patients gave their oral assent to participate in the study.

After treatment with pramipexole, 13 of the 22 patients experienced complete or impressive alleviation of their depressive state; six were taking pramipexole alone, and seven had pramipexole added to their current antidepressant regimen, which had previously been ineffective. In five other patients, the illness was more complex and usually involved cycling—rapid or intermediate—accompanying borderline personality or bipolar disorder. Pramipexole contributed significantly to alleviation of the depressive component of the illness, but that was not enough to resolve the complex clinical picture of these five patients. One patient had to stop taking the drug at a dose of 3 mg/day because of unacceptable side effects; he received no therapeutic benefit at lower doses. Three patients could not tolerate the drug at all. In all, five patients could take no more than 0.5 mg/day or did well with less, four did well taking 0.5–1.0 mg/day, eight required 1–3 mg/day, and five required more than 3 mg/day. No patient took more than 4.5 mg/day.

The study group included three women who could tolerate no antidepressants; neither could they tolerate pramipexole. One complained of confusion, a second of sleepiness, and a third of "wired" and "spacey" sensations. For two of the women, even a small fraction of a tablet produced side effects. The other woman took no more than 0.5 mg t.i.d.

It was necessary in most cases to increase the dose over time as tolerance developed. However, tolerance did not develop any more quickly than with other antidepressants. Whenever a patient reached a maximum dose of 4.5 mg/day of pramipexole, if it was necessary to augment the dose, I added another antidepressant. In no case did pramipexole seem to become completely ineffectual. Side effects were rel-

atively few and included nausea, sleepiness, and unremitting alertness, which for some patients led to a sleep deficit.

I infer from this study that pramipexole possesses significant antidepressant potency and is no less effective than any of the other antidepressants in use. It has relatively few side effects, has high patient acceptability, and is no more likely to require larger doses than any other antidepressant. I hesitate to prescribe it as a first-line treatment for depression because patients do not welcome having to take medication three times a day.

Recently, I have been prescribing ropinirole, which is similar to pramipexole except that it possesses some opioid characteristics. In the few months that I have been prescribing it, I find that patients prefer it to pramipexole and that it is more likely to raise self-esteem than pramipexole or conventional antidepressants. However, it seems to induce sleepiness as a side effect more often than does pramipexole.

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## Benzodiazepine Discontinuation in Generalized Anxiety Disorder

TO THE EDITOR: In an interesting study, Kark Rickels, M.D., et al. (1) demonstrated the usefulness of imipramine in a benzodiazepine discontinuation program for patients with generalized anxiety disorder. Low anxiety scores (Hamilton Anxiety Rating Scale score: mean=12.5, SD=6.3) at baseline and at the 12-month follow-up and the fact that only 11 (21.2%) of 52 patients required pharmacotherapy (tricyclic antidepressants or selective serotonin reuptake inhibitors) to treat their anxiety symptoms makes one suspect that the majority of the subjects had either a mild form of generalized anxiety disorder or benzodiazepine dependence. This poses a limitation on the generalizability of the results. Maintenance therapy for generalized anxiety disorder is recommended for at least 1 year after control of anxiety symptoms has been achieved (2), and benzodiazepine dependence is known to occur at therapeutic doses (3).

Dr. Rickels et al. considered the study group "rather treatment resistant" (1, p. 1978) on the basis of previous discontinuation attempts. However, these attempts were without any apparent therapeutic intervention. The use of nonpharmacological and pharmacological measures is an important factor in determining the success of benzodiazepine discontinuation (3). The dissatisfaction of the majority of the patients (75.7%) with benzodiazepine therapy for the management of anxiety may have been a motivating factor in these discontinuation attempts. Another argument against treatment resistance is the benzodiazepine-free status of 37.5% of the patients after 3 months of taking placebo alone.

We notice certain issues regarding the methods that might have had a bearing on the results of this study. It was not clarified in the article how the subjects were assigned to three study groups and whether random assignment was carried out to reduce rater or response bias. Moreover, the patients taking imipramine experienced side effects that could have compromised the study blind. The description of the 12-month follow-up assessment contains no mention of the differences among the three treatment groups regarding their benzodiazepine-free status. Logistic regression analysis showed that lower levels of baseline anxiety symptoms predicted a successful taper at 3 months. Baseline depressive symptoms were not analyzed, even though both anxiety *and* depressive symptoms were hypothesized to play an important part in benzodiazepine withdrawal (1). The 41.2% (seven of 17) of patients taking benzodiazepines at 3 months but not at 12 months might actually be lower, since the patients taking benzodiazepines at 3 months were more likely to drop out of follow-up by 12 months than the benzodiazepine-free patients (odds ratio=3.7).

Notwithstanding issues regarding conception and methods, this study opens up new avenues in tackling benzodiazepine dependence in long-term benzodiazepine users.

### References

1. Rickels K, DeMartinis N, García-España F, Greenblatt DJ, Mandos LA, Rynn M: Imipramine and buspirone in treatment of patients with generalized anxiety disorder who are discontinuing long-term benzodiazepine therapy. Am J Psychiatry 2000; 157: 1973–1979
2. Papp LA: Anxiety disorders: somatic treatment, in Comprehensive Textbook of Psychiatry. Edited by Sadock BJ, Sadock VA. Philadelphia, Lippincott Williams & Wilkins, 2000, pp 1490–1497
3. Juergens SM: Benzodiazepines and addiction. Psychiatr Clin North Am 1993; 16:75–86

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## Dr. Rickels and Colleagues Reply

TO THE EDITOR: We thank Drs. Gupta, Gupta, and Avasthi for commenting on our data. Dr. Gupta et al. point out that the different attrition rates of the patients who were and were not taking benzodiazepines 3 months after the taper may have affected our success rates at 12 months. Indeed, this was true for the patients taking benzodiazepines but not for the patients who were free of benzodiazepines at 3 months. When we carried forward 3-month data to 12 months for the patients who were not available at the 12-month follow-up, our rate of successful tapers remained at 83% for the patients who were not taking benzodiazepines at 3 months, but it decreased from 41.2% to 25.0% for the patients who were taking benzodiazepines at 3 months. The use of a data set from the last observation carried forward thus leads to a lower rate of success at 12 months than was originally reported for the patients who were unsuccessful in their taper attempt, making our rates of successful benzodiazepine taper even more remarkable.

We apologize for not having used the phrase "random assignment" when describing our double-blind treatment methods. Indeed, the patients were assigned to the three treatments according to a random-assignment schedule, which resulted in three treatment groups of equal sizes. In terms of potential predictors of a successful taper, Dr. Gupta et al. wonder why we did not use the level of baseline symptoms as a potential predictor. We did not do so because depressive symptoms at baseline did not correlate significantly ($p<0.10$) with treatment outcome and, thus, as we stated in the article, did not fulfill our criteria for variables entered into the logistic regression analysis. We believe that the other com-

ments made by Dr. Gutpa and colleagues, as they relate to the study group, the generalizability of the results, benzodiazepine dependence, long-term treatment for generalized anxiety disorder, resistance to benzodiazepine therapy, and the effect of treatment group on benzodiazepine status at 12 months, were adequately covered in the article.

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## Early Onset of Schizophrenia

TO THE EDITOR: We read with great interest the article by Carole Di Maggio, M.D., and her colleagues (1). Although the study presented some interesting data about decreasing age at onset of schizophrenia, it also raised some questions about the interpretation and analyses of the data. The authors presented retrospective data for medical records (N=877) from 1976, 1986, and 1996. Individuals in the study were divided into three birth cohorts: 1905–1944, 1945–1964, and 1965–1984. However, the significant decrease in age at onset through time could be due to bias caused by the different age structures of the cohorts. Individual ages of the subjects in the 1905–1944 cohort were from 32 to 91 years, the subjects in the 1945–1964 cohort were aged 12 to 51 years, and the subjects in the 1965–1984 cohort were aged 1 to 31 years. Thus, all persons who died before the age of 32 could not be part of the 1905–1944 cohort. This might have been an important source of bias in the study because mortality is greater for patients with schizophrenia, but at the population level, the standardized mortality ratio for schizophrenia decreases exponentially with age (2). Only patients with illness onset before age 32 could be present in the youngest cohort.

We calculated mean ages at onset on the basis of our data (3) for cohorts from 1950–1955 (N=4,023) and 1956–1961 (N=2,941), with follow-up assessments made, respectively, at 1969–1978 and 1975–1984. The mean ages at onset were 21.8 and 21.9 years. We suggest that the data presented by Dr. Di Maggio and colleagues should be reanalyzed with consideration of the different age structures.

### References

1. Di Maggio C, Martinez M, Ménard JF, Petit M, Thibaut F: Evidence of a cohort effect for age at onset of schizophrenia. Am J Psychiatry 2001; 158:489–492
2. Brown S: Excess mortality of schizophrenia: a meta-analysis. Br J Psychiatry 1997; 171:502–508
3. Suvisaari J, Haukka JK, Tanskanen AJ, Lönnqvist JK: Decline in the incidence of schizophrenia in Finnish cohorts born from 1954 to 1965. Arch Gen Psychiatry 1999; 56:733–740

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## Dr. Di Maggio and Colleagues Reply

TO THE EDITOR: We calculated mean ages for the cohorts in our study, taking into account their different age structures. For the third cohort (1965–1984), the maximum age of the individuals was 29 (born in 1967 and hospitalized in 1996.)

In order to take this bias into account, we analyzed the data for only the patients with an onset before age 29 in the three cohorts. The cohort effect remained among the three groups, showing an increasingly lower age at onset of first psychotic symptoms from the first cohort (1905–1944) (23 years) to the third cohort (1965–1984) (20 years) and no effect of gender ($p<0.00005$).

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## Quetiapine and Cataracts

TO THE EDITOR: Cautiousness is an appropriate response to the letter by Fakhrudin Valibhai, Pharm.D., et al. (1). First, Mr. A's lens changes were not representative of the most common forms of lens opacity, which are usually ascribed to lens toxins. Nor were they a type of lens opacity that is subject to reliable and consistent ascertainment. In fact, it has proven so difficult to evaluate minor lens opacities, such as the cortical vacuoles noted in Mr. A, that the most-accepted lens opacity classification system (Lens Opacities Classification System III) largely ignores them in favor of the more reliable ascertainment of cortical wedges and spokes (2).

Perhaps more important, the authors' assertion that Mr. A did not have any other risk factors is mistaken. Although their MEDLINE search "of articles on the patient's other medications revealed no association with cataracts" (1, p. 966), an abundant literature nevertheless exists on the association of agents used to treat schizophrenia and lens opacities. For instance, haloperidol, one of the agents used to treat Mr. A, has a recognized association with capsular cataracts after long-term therapy (3). Phenothiazines, also used to treat Mr. A, are recognized as causing deposits to form within the lens (4). Moreover, Isaac et al. (5) reported that the lens changes induced by phenothiazines are clearly deleterious. McCarty et al. (6) raised the suspicion that schizophrenia itself might be a risk factor for cataracts. Since poor nutrition is also a risk factor for cataracts (7), it is difficult to tell whether lens opacity is a manifestation of the biology of schizophrenia or of poor eating habits.

Taken together, multiple and diverse risk factors existed for Mr. A's cataracts. That cataracts most often develop slowly and over long durations undermines any presumption of a specific attribution for the lens changes observed in Mr. A. With so many confounding variables, it impossible to determine a single cause of Mr. A's cataracts. Moreover, in my 3-year surveillance of ocular safety for AstraZeneca, which markets quetiapine, I have seen no clear signal emerge for toxicity in any part of the eye.

### References

1. Valibhai F, Phan NB, Still DJ, True J: Cataracts and quetiapine (letter). Am J Psychiatry 2001; 158:966
2. Chylack LT Jr, Wolfe JK, Singer DM, Leske MC, Bullimore MA, Bailey IL, Friend J, McCarthy D, Wu SY (The Longitudinal Study of Cataract Study Group): The Lens Opacities Classification System III. Arch Ophthalmol 1993; 111:831–836

3. Honda S: Drug-induced cataract in mentally ill subjects. Jpn J Clin Ophthalmol 1974; 28:521–526
4. Margolis LH, Gobic JL: Lenticular opacities with prolonged phenothiazine therapy. JAMA 1965; 193:7–9
5. Isaac NE, Walker AM, Jick H, Gorman M: Exposure to phenothiazine drugs and risk of cataract. Arch Ophthalmol 1991; 109: 256–260
6. McCarty CA, Wood CA, Fu CL, Livingston PM, Mackersey S, Stanislavsky Y, Taylor HR: Schizophrenia, psychotropic medication, and cataract. Ophthalmology 1999; 106:683–687
7. Jacques PF, Hartz SC, Chylack LT Jr, McGandy RB, Sadowski JA: Nutritional status in persons with and without senile cataract: blood vitamin and mineral levels. Am J Clin Nutrition 1988; 48: 152–158

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## Clozapine and Suicide

TO THE EDITOR: Michael J. Sernyak, M.D., et al. (1) reported that they found no evidence that clozapine reduces the rate of suicide and rejected the evidence from other authors that clozapine reduces the rates of suicide attempts and completions. Their arguments for rejecting the findings of the previous studies require careful scrutiny. Dr. Sernyak et al. claimed that there was no control group in the study by Meltzer and Okayli (2), in which the rate of suicide attempts in the 2 years after clozapine treatment was initiated was 86% less than in the same patients in the 2 years before they began taking clozapine. Thus, each patient acted as his or her own comparison subject. Although this design is not as robust as a randomized, parallel-group, double-blind study, it is incorrect to describe it as having no comparison group. Moreover, the statement that the decrease in the rate of suicide attempts could represent regression to the mean needs clarification because there is no evidence that the mean rate of suicide attempts was higher than normal in the period before the subjects started taking clozapine.

Dr. Sernyak et al. also incorrectly characterized the study by Walker et al. (3) as having no "control group of similar patients not exposed to clozapine" and as employing a comparison group of patients who had stopped taking the medication and who would have been expected to "have a poorer clinical outcome" (1, p. 931). The comparison group in the study by Walker et al. (3) comprised patients who had recently begun taking clozapine, a clear indication of similarity with those who continued to take clozapine. There was no evidence to support the authors' conclusion that the patients who stopped taking clozapine were at greater risk for suicide. The standardized mortality rate of the comparison group (13.9) was well within the expected limits for patients with schizophrenia. The standardized mortality rate for the patients treated with clozapine was 2.27, which falls well outside the confidence interval of that for patients with schizophrenia, which has been reported to range from 9 to 20 in most studies.

Next, Dr. Sernyak et al. dismissed the data from Reid et al. (4), which showed that the rate of suicide in clozapine-treated patients in the Texas Department of Mental Health and Mental Retardation was 12.7 out of 100,000 compared to 60–63 out of 100,000 of those not treated with clozapine, with the argument that no data were presented for basic demographic factors, such as age, gender, and race. There was no evidence that these differed in the two groups. The authors also failed to include a study by Munro et al. (5), who reported that the standardized mortality rate in the entire Clozaril National Registry in Great Britain was 4.98, compared with a standardized mortality rate of 20 from other published studies of the general schizophrenia patient group. Both Meltzer and Okayli (2) and Reid et al. (4) reported similar data from the U.S. Clozaril National Registry from two different time periods. It is remarkable that all six of these studies showed a 75%–86% decrease in the rates of suicide attempts or completions after clozapine treatment. It is noteworthy that Dr. Sernyak et al. found a nearly significant effect of clozapine in reducing the rate of suicide in those who took clozapine for part, let alone, all of the period that they were at risk.

### References

1. Sernyak MJ, Desai R, Stolar M, Rosenheck R: Impact of clozapine on completed suicide. Am J Psychiatry 2001; 158:931–937
2. Meltzer HY, Okayli G: Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. Am J Psychiatry 1995; 152:183–190
3. Walker AM, Lanza LL, Arellano F, Rothman KJ: Mortality in current and former users of clozapine. Epidemiology 1997; 8: 671–677
4. Reid WH, Mason M, Hogan T: Suicide prevention effects associated with clozapine therapy in schizophrenia and schizoaffective disorder. Psychiatr Serv 1998; 49:1029–1033
5. Munro J, O'Sullivan D, Andrews C, Arana A, Mortimer A, Kerwin R: Active monitoring of 12,760 clozapine recipients in the UK and Ireland: beyond pharmacovigilance. Br J Psychiatry 1999; 175:576–580

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TO THE EDITOR: Dr. Sernyak et al. claimed that their results failed to support the hypothesis that clozapine treatment is associated with significantly fewer deaths due to suicide. The effect of clozapine on all causes of mortality, including suicide, was compared in a study with a group chosen by the use of "propensity scaling," a potentially problematic method that has severe limitations in this instance. It is a matter of concern that the variables available for subject matching did not include the four most important characteristics necessary for matching for suicide risk, i.e., the number, timing, and lethality of prior suicide attempts and the severity of depression at index admission. None of the variables used to create the comparison group, with the exception of substance abuse, is relevant to suicidality. This makes it difficult to be confident that the two groups had equivalent risks for suicide.

Dr. Sernyak et al. used data from a study by a colleague and me (Meltzer and Okayli, 1995) to conclude that treatment resistance is the most relevant factor in the matching process even though our finding was that there was no difference in the rate of suicidality between treatment-resistant and nonresistant patients. Furthermore, because the Department of Veterans Affairs (VA) policy of minimizing the use of clozapine led to clozapine use in 1% versus 6%–8% of non–VA patients with schizophrenia, the clozapine-treated patients in this study may not be representative of general users of clozapine in four previous studies (Meltzer and Okayli, 1995; Walker et al., 1997; Reid et al., 1998; and Munro et al., 1999)

that showed a 70%–86% decrease in the rate of suicide attempts or completions.

However, what is even more troublesome is that the authors assumed that any effect of clozapine on suicide, no matter how briefly clozapine was administered, should be expected to decrease the rate of suicide for up to 6 years! Dr. Sernyak et al. included all of the patients with schizophrenia who received clozapine through the VA *for any period of time* between fiscal years 1992 and 1995. They used the National Death Index to determine all causes of death, including suicide, from the time the patients started clozapine treatment until Dec. 31, 1998. Thus, they included patients who were treated with clozapine for less than 12 months or for an unknown period of more than 12 months during 1992–1998, whereas they could easily have restricted their analysis to the time in which clozapine was prescribed to the patients. An unknown number of patients in the clozapine-treated groups—probably the majority—were not taking clozapine for most of the outcome period.

Nevertheless, the authors still concluded that clozapine reduced the rate of suicide, which they failed to bring to the attention of readers. According to Table 2 in their article, five of 1,018 patients treated with clozapine for more than 12 months committed suicide, compared to 23 of 2,380 of the subjects in the comparison group ($\chi^2$=2.77, df=1, p=0.10). Given that four previous studies indicated that clozapine reduced the rate of suicide by 70% to 86%, it is unfortunate that the authors chose not to call attention to their finding that, at the least, constitutes a strong trend to support the idea that clozapine reduces the rate of suicide. In any event, since a change of one or two in the number of suicides in either group would dramatically change the results in this analysis, this study does little to affect confidence in the abundant evidence that clozapine reduces the suicide rate.

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## Dr. Sernyak and Colleagues Reply

TO THE EDITOR: We welcome the chance to respond to the questions raised by Drs. Ertugrul and Meltzer because it provides us with an additional opportunity to explain why we feel our assessment that clozapine is not associated with a lower than usual risk of suicide is based on a more sound evaluation method than in previous studies.

Dr. Ertugrul's letter confirms our primary claim that previous studies of this issue have employed mostly weak designs. The most informative control groups had characteristics demonstrably similar to those of the specified treatment groups in every respect except treatment assignment. As summarized by Dr. Ertugrul, previous studies have employed historical control groups (Meltzer and Okayli, 1995), control groups about which so little is known that comparability could not be assessed (Reid et al., 1998), and control groups that have included no patients who were not previously exposed to clozapine (Walker et al., 1997). Thus, we feel that Dr. Ertugrul's comments provide substantial support for our evaluation of the literature.

Dr. Meltzer asserts that we did not match for the "four most important" variables for the matching for suicide risk in patients with schizophrenia. While we agree that this is a limitation, as discussed at length in our article, it applies to all of the studies on this subject. Dr. Meltzer draws special attention to the fact that when the patients never exposed to clozapine were compared with the patients who had been receiving clozapine for more than 12 months (groups that exclude many who showed no improvement while taking clozapine), there was a trend (at the p=0.10 level) for those receiving clozapine to have a lower rate of suicide. We do not think this was a relevant comparison for evaluating the effect of clozapine on suicidal risk.

The comparison that best reflects clinical practice and is most informative compares all patients who received clozapine with a carefully matched group of patients who were never exposed to clozapine, yielding a nonsignificant (p=0.76) difference in the rates of suicide. We presented the comparison between those who completed 1 year of treatment (excluding a large number of treatment nonresponders) and the entire control group (from which nonresponders had not been excluded) to illustrate the bias inherent in previous studies comparing patients who dropped out of treatment and those who continued. The fact that this highly biased comparison still failed to yield a significantly lower rate of suicide in our study adds further support to the nonsignificant findings of our main analysis.

We appreciate the thoughtful comments of our colleagues, which allowed us to emphasize and further clarify some of the more informative points of our analysis.

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## Clozapine and Dopamine $D_2$ Blockade

TO THE EDITOR: Mirjam Talvik, M.D., et al. (1) asserted that there is "no support" for the regionally selective action of clozapine at dopamine $D_2$ receptors. Much evidence contradicts this view. Chronic treatment with clozapine (in contrast to treatment with classical antipsychotic drugs) up-regulates cortical $D_2$ receptors at doses that do not affect striatal receptors. Dopamine turnover is also increased by clozapine in the cortex but not in the striatum (2). Our [$^{123}$I]epidepride single photon emission computerized tomography (SPECT) studies have shown that clozapine preferentially blocks temporal cortical, over striatal $D_2$, receptors. $D_2$ occupancy by classical antipsychotic drugs has been shown as not regionally selective (3). Dr. Talvik and colleagues suggested methods limitations (which we discuss comprehensively) in our earlier studies, rendering these findings inconclusive. Nevertheless, they did not cite two short positron emission tomography (PET) reports. These independent studies, using fully validated, long-lived PET probes and quantitative single-tracer PET protocols—[$^{76}$Br]FLB 457 and [$^{18}$F]epidepride—have substantiated our data for clozapine and olanzapine, respectively (4, 5). Dr. Talvik et al. (1) now supply findings to the contrary. The reason for discrepant results awaits elucidation. Possibilities include variability in ligand kinetics, the sensitivity of different ligands to regional dopamine concentrations, or receptor status. The majority of in vitro animal and human data still favor a selective action of clozapine at limbic cortical $D_2$ receptors.

This issue remains unresolved in vivo, to be clarified by further studies.


### References

1. Talvik M, Nordström A-L, Nyberg S, Olsson H, Halldin C, Farde L: No support for regional selectivity in clozapine-treated patients: a PET study with [$^{11}$C]raclopride and [$^{11}$C]FLB 457. Am J Psychiatry 2001; 158:926–930
2. Lidow MS, Williams GV, Goldman-Rakic PS: The cerebral cortex: a case for a common site of action of antipsychotics. Trends Pharmacol Sci 1998; 19:136–140
3. Bigliani V, Pilowsky LS: The in vivo neuropharmacology of schizophrenia. Br J Psychiatry 1999; 174(suppl 38):23–34
4. Xiberas X, Martinot JL, Mallet L, Artiges E, Loc'H C, Maziere B, Paillere-Martinot ML: Extrastriatial and striatal D(2) dopamine receptor blockade with haloperidol or new antipsychotic drugs in patients with schizophrenia. Br J Psychiatry 2001; 179:503–508
5. Meltzer HY, Park S, Kessler R: Cognition, schizophrenia, and the atypical antipsychotic drugs. Proc Natl Acad Sci 1999; 96: 13591–13593



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## Dr. Talvik and Colleagues Reply

TO THE EDITOR: Drs. Pilowsky and Ell claim that clozapine treatment induces regionally selective occupancy of $D_2$ receptors in vivo. In our study we did not find support for regional selectivity. We agree with Drs. Pilowsky and Ell that this issue needs to be clarified.

Using the high-affinity PET radioligand [$^{11}$C]FLB 457, a close analog of the SPECT ligand [$^{123}$I]epidepride, we were initially puzzled by images that gave the impression of higher occupancy in extrastriatal regions. This unexpected observation was made for patients treated with clozapine and patients treated with low doses of haloperidol and seemed to be confirmed when ratio analyses were applied for the calculation of $D_2$ occupancy. However, this finding was not confirmed when we used [$^{11}$C]raclopride for striatal binding. We recently conducted a study that suggests methods limitations as a possible reason for the discrepant results (1).

When ratio approaches are used to obtain reliable estimates for binding potential, the radioactivity must reach equilibrium during the acquisition time. The problem is that the time to reach equilibrium is highly dependent on the density of $D_2$ receptors, which varies about 100-fold in the human brain. A consequence is that regions with low receptor density (i.e., the temporal cortex) will reach equilibrium long before regions with high receptor density (i.e., the striatum). As shown in simulations based on experimental data, the end-time method, a ratio method used in SPECT, overestimates the binding potential if the time to equilibrium is within the time of data acquisition but underestimates the binding potential if the time to equilibrium falls beyond the acquisition time (1). In SPECT studies using this method, low striatal and high extrastriatal binding potential have been reported (2, 3). In the reports of the PET studies referred to in the letter, the methods were not reported in detail, which makes it difficult to appraise the results (Meltzer et al., 1999; Xiberas et al., 1999). It cannot be discounted that these results were also influenced by the methods limitations of applying a ratio analysis on striatal binding at pre-equilibrium conditions.


### References

1. Olsson H, Farde L: Potentials and pitfalls using high affinity radioligands in PET and SPET determinations on regional drug induced D2 receptor occupancy—a simulation study based on experimental data. Neuroimage 2001; 14:936–945
2. Pilowsky LS, Mulligan RS, Acton PD, Ell PJ, Costa DC, Kerwin RW: Limbic selectivity of clozapine (letter). Lancet 1997; 350:490–491
3. Bigliani V, Mulligan RS, Acton PD, Ohlsen RI, Pike VW, Ell PJ, Gacinovic S, Kerwin RW, Pilowsky LS: Striatal and temporal cortical D2/D3 receptor occupancy by olanzapine and sertindole in vivo: a [123I]epidepride single photon emission tomography (SPET) study. Psychopharmacology (Berl) 2000; 150:132–140



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## Outcome of Asperger's Syndrome

TO THE EDITOR: The study by Peter Szatmari, M.D., et al. (1) is a laudable endeavor. Although the authors found no data on the outcome of children with Asperger's syndrome, Asperger, as cited by Wing (2), emphasized the stability of the clinical picture throughout childhood and adolescence and at least into early adult life, with maturation bringing about an increase in skill level. This study thus confirms, in part, the original observation. Still, there is a paucity of information on the outcome of this disorder in late life.

Another aspect relevant to outcome in Asperger's syndrome is its psychiatric comorbidity. Comorbid disorders are increasingly being recognized in patients with Asperger's syndrome (3). It would be interesting to know how comorbidity modifies the course and prognosis of Asperger's syndrome. We have observed patients with Asperger's syndrome developing bipolar disorder in late adolescence and early adulthood and responding well to treatment with mood stabilizers. There is some literature suggesting an etiological link between the two conditions (4).

As is implicit in the article, the DSM-IV criteria for Asperger's syndrome require a change. Relaxation of the criterion for qualitative impairment in social interaction vis-à-vis autistic disorder and the inclusion of features common in Asperger's syndrome, such as pragmatically impaired speech and motor clumsiness, can be envisaged.

Another issue worth highlighting is the stability of neuropsychological deficits in Asperger's syndrome. While using the Luria Nebraska Neuropsychological Battery, we observed impairment in more than one brain region (5). Hence, comprehensive neuropsychological assessment and its correlation with other outcome measures in Asperger's syndrome are encouraged.


### References

1. Szatmari P, Bryson SE, Streiner DL, Wilson F, Archer L, Ryerse C: Two-year outcome of preschool children with autism or Asperger's syndrome. Am J Psychiatry 2000; 157:1980–1987

2. Wing L: Asperger's syndrome: a clinical account. Psychol Med 1981; 11:115–129
3. Gillberg C, Billstedt E: Autism and Asperger syndrome: coexistence with other clinical disorders. Acta Psychiatr Scand 2000; 102:321–330
4. DeLong R: Children with autistic spectrum disorder and a family history of affective disorder. Dev Med Child Neurol 1994; 36: 674–687
5. Duggal HS, Dutta S, Sinha VK, Basu S, Pandey S, Nizamie SH, Nizamie A: Neurobiology of Asperger's syndrome: a case study and overview. Indian J Psychiatry 2001; 43:267–272

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