

Letters to the Editor

Mechanisms of Weight Gain Induced by Antipsychotic Drugs

Sir: Casey and Zorn¹ recently published an excellent review article on the mechanisms of body weight gain induced by antipsychotic drugs. It is a timely topic, given the growing concern of the psychiatric community about the risk of obesity and non-insulin dependent diabetes mellitus during treatment with antipsychotics, particularly with some of the new atypical agents.^{2,3}

Surprisingly, the authors did not mention a considerable body of research on the subject, conducted at our laboratory at Los Andes University Medical School in Merida, Venezuela, in collaboration with the National Institute of Mental Health, Bethesda, Md., and Princeton University, Princeton, N.J. We have studied the effects of the antipsychotic sulpiride on body weight gain and feeding regulation in rats and humans, and, in fact, our research is the only published animal model of antipsychotic-induced obesity. I would like to summarize our findings within a chronological perspective, so that your readers may use them to complement the information provided by Casey and Zorn.

When we first tested in Wistar rats the effects of most available antipsychotics in the 1980s, one striking finding was that significant body weight gain was observed only in females and prepubertal males.^{4,5} This sex-dependent effect was replicated by other authors⁶ and has also been reported with risperidone.⁷ Even though significant body weight gain was observed after administration of haloperidol, trifluoperazine, and thioridazine in female rats, the effect was more robust with racemic sulpiride, a D₂-D₃ dopamine receptor antagonist. Hence, we used this agent for additional experiments. Body weight gain during sulpiride administration was dose dependent,⁴ required increased food intake in order to be observed,⁸ and was prevented by bromocriptine.^{4,9,10} As sulpiride injections in the lateral-perifornical hypothalamus induced strong feeding and drinking in satiated rats,^{4,11,12} we suggested that blockade of D₂ receptors in that brain area might mediate antipsychotic effects on feeding.⁴ This proposal was contradicted for 2 main reasons: (1) the strong sex-dependent effect observed in rats in the absence of evidence of gender-related hypothalamic mechanisms for feeding regulation and (2) systemic sulpiride did not counteract the anorexia induced by local hypothalamic injections of amphetamine in rats.¹³ The role of dopamine in feeding regulation was also challenged by Silverstone et al.,¹⁴ because pimozide did not prevent amphetamine anorexia in healthy people. In 1995, Parada et al.¹⁵ showed that rats self-inject sulpiride in the lateral-perifornical hypothalamus. In addition, these injections induce dopamine release in the nucleus accumbens, suggesting it might be an important pathway for food reward related to D₂-D₃ receptors in the lateral-perifornical hypothalamus.

In 1989, Parada et al.¹⁶ proposed that antipsychotic-induced body weight changes in rats might be mediated by hyperprolactinemia-induced hypogonadism. It could explain

sulpiride-induced body weight gain and permanent diestrus in females and body weight loss in males treated with some antipsychotics.^{4,5,14} In support of their proposal, we showed that estradiol and tamoxifen (an agonist of estradiol in relation to food intake in rodents) prevented sulpiride-induced body weight gain in female rats.^{10,16} In addition, ovariectomized rats (which display obesity after ovary removal) did not gain additional body weight after sulpiride administration.¹⁶

Our research group has also studied the role of hypogonadism in antipsychotic-induced body weight gain in people during treatment with typical antipsychotics. Sulpiride, phenothiazines, and haloperidol induce a strong reduction in the serum levels of estradiol and progesterone after short-term treatment.^{17,18} However, after prolonged administration, estradiol (but not progesterone) levels normalize.^{19,20} Hence, hypoenestrogenemia might be involved in the initial events leading to body weight gain; low progesterone levels might promote abdominal obesity, as suggested by Björntorp.²¹ Low serum testosterone levels in men, which promote adiposity, have been observed after short-term administration of phenothiazines and haloperidol (but not sulpiride).^{18,22} That hormone has not been explored following prolonged antipsychotic administration. An important unresolved issue is that low gonadal steroid levels in people with schizophrenia may be relatively independent of antipsychotic administration.²³

An additional role for hyperprolactinemia may be the modulation of insulin sensitivity,²³ which is a very important issue, given the propensity of antipsychotics to induce glucose intolerance and non-insulin dependent diabetes mellitus.

Female rats with sulpiride-induced body weight gain display other interesting features: they have normal or low glucose and insulin levels and normal leptin levels.^{8,24,25} This endocrine/metabolic profile differs considerably from that reported in obese people after treatment with typical or atypical antipsychotics, who display the expected high levels of glucose, insulin, and leptin.^{19,20,26} Interestingly enough, male Wistar rats treated with sulpiride for 21 days did not gain body weight (as expected) and had significantly high levels of glucose and insulin after a glucose overload.²⁷ This suggests insulin resistance (which may prevent body weight gain) and is in clear contrast to the metabolic profile observed in females. Finally, sulpiride-induced body weight gain in rats was not counteracted by pharmacologic doses of amantadine or naltrexone.^{9,28}

In summary, the interaction of antipsychotics with dopamine receptors in the lateral-perifornical hypothalamus may stimulate appetite. This effect is perhaps balanced by the blockade of dopamine receptors in the limbic system, which, rather, decreases feeding. However, the interaction of antipsychotics with lateral-perifornical hypothalamus neurons may play a role in the voracious appetite observed in some patients shortly after antipsychotic administration.²⁹ An insufficient number of D₂ striatal receptors may be involved in primary obesity.³⁰ This might be mimicked by antipsychotic-induced blockade of these receptors.

The role of prolactin and the relative hypogonadism is an open question, and most of our work has been inferential and correlative. Prolactin is worth investigating because the typical antipsychotics will still be used for a long time,³¹ and some of the new atypical agents may induce discrete and short-lasting (olanzapine and clozapine) or robust hyperprolactinemia (risperidone). It is possible that this small elevation in prolactin may still be active regarding body weight regulation or may have sensitizing effects. It might be particularly interesting to test this hypothesis in patients who are homozygotes for the A₁ allele of the dopamine receptor and may be particularly sensitive to the effects of prolactin.³²

Allison and Casey³³ in an article that was published in the same supplement as the Casey and Zorn article are right when they state that this is an understudied subject that requires more attention from the psychiatric community.

Dr. Baptista reports no affiliation or relationship to disclose relevant to the subject matter of this letter.

Drs. Casey and Zorn were shown this letter and declined to comment.

REFERENCES

- Casey DE, Zorn SH. The pharmacology of weight gain with antipsychotics. *J Clin Psychiatry* 2001;62(suppl 7):4–10
- Green AI, Patel JK, Goisman RM, et al. Weight gain from novel antipsychotic drugs: need for action. *Gen Hosp Psychiatry* 2000; 22:224–235
- Masand PS, Gupta S. Long-term adverse effects of novel antipsychotics. *J Psychiatr Pract* 2000;11:299–309
- Baptista T, Parada M, Hernández L. Long term administration of some antipsychotic drugs increases body weight and feeding in rats: are D₂ dopamine receptors involved? *Pharmacol Biochem Behav* 1987;27:399–405
- Baptista T, Parada MA, Murzi E. Puberty modifies sulpiride effects on body weight in rats. *Neurosci Lett* 1988;92:161–164
- Shimizu H, Shimomura Y, Uehara Y, et al. Involvement of sex hormone in body weight gain by selective D₂ antagonist sulpiride. *Exp Clin Endocrinol* 1990;96:25–29
- Risperdal [product monograph]. Toronto, Ontario, Canada: Janssen-Ortho, Inc; 2000
- Baptista T, Teneud L, Contreras Q, et al. Mechanism of the neuroleptic-induced obesity in rats. *Prog Neuropsychopharmacol Biol Psychiatry* 1998;22:187–198
- Baptista T, López MA, Teneud L, et al. Amantadine in the treatment of neuroleptic-induced obesity in rats: behavioral, endocrine and neurochemical correlates. *Pharmacopsychiatry* 1997;30:43–54
- Baptista T, Araujo de Baptista E, Weiss S, et al. Tamoxifen prevents sulpiride-induced weight gain in female rats. *Pharmacol Biochem Behav* 1997;57:215–222
- Parada MA, Hernández L, Hoebel BG. Sulpiride injections in the lateral hypothalamus induce feeding and drinking in rats. *Pharmacol Biochem Behav* 1988;30:917–923
- Baptista T, Teneud L, Hernández L. Enhancement of amphetamine anorexia after chronic administration of sulpiride in rats. *Pharmacol Biochem Behav* 1993;45:45–49
- Parada MA, Puig de Parada M, Hernández L, et al. Ventromedial hypothalamus vs lateral hypothalamic D₂ satiety receptors in the body weight increase induced by systemic sulpiride. *Physiol Behav* 1991;50:1161–1165
- Silverstone T, Finchman J, Wells B, et al. The effect of the dopamine receptor-blocking drug pimozone on the stimulant and anorectic actions of dextroamphetamine in man. *Neuropharmacology* 1980;19:1235–1237
- Parada MA, Puig de Parada M, Hoebel BG. Rats self-inject a dopamine antagonist in the lateral hypothalamus where it acts to increase extracellular dopamine in the nucleus accumbens. *Pharmacol Biochem Behav* 1995;52:179–187
- Parada MA, Hernández L, Páez X, et al. Mechanism of the body weight increase induced by systemic sulpiride. *Pharmacol Biochem Behav* 1989;33:45–50
- Baptista T, Molina MG, de Quijada M, et al. Effects of the antipsychotic drug sulpiride on reproductive hormones in healthy women: relationship with body weight regulation. *Pharmacopsychiatry* 1997;30:256–262
- Baptista T, Reyes D, Hernández L. Antipsychotic drugs and reproductive hormones: relationship to body weight regulation. *Pharmacol Biochem Behav* 1999;62:409–417
- Baptista T, Lacruz A, Silvera R, et al. Body weight gain after administration of antipsychotic drugs: correlation with leptin, insulin and reproductive hormones. *Pharmacopsychiatry* 2000;33:81–88
- Baptista T, Lacruz A, Angeles F, et al. Endocrine and metabolic profile in the obesity associated to typical antipsychotic drug-administration. *Pharmacopsychiatry* 2001;34:223–231
- Björntorp P. Regional obesity. In: Björntorp P, Brodoff BN, eds. *Obesity*. Philadelphia, Pa: JB Lippincott; 1992:579–586
- Baptista T, Alastre T, Contreras Q, et al. Effects of the antipsychotic drug sulpiride on reproductive hormones in healthy men: relationship with body weight regulation. *Pharmacopsychiatry* 1997;30:250–255
- Baptista T. Body weight gain induced by antipsychotic drugs: mechanisms and management. *Acta Psychiatr Scand* 1999;100:3–16
- Baptista T, Alvarez L, Lacruz A, et al. Glucose tolerance and serum insulin levels in an animal model of obesity induced by sub-acute or chronic administration of antipsychotic drugs. *Prog Neuropsychopharmacol Biol Psychiatry* 1999;23:277–287
- Lacruz A, Baptista T, de Mendoza S, et al. Antipsychotic drug-induced obesity in rats: correlation between leptin, insulin and body weight during sulpiride treatment. *Mol Psychiatry* 2000;5:70–76
- Melkersson KI, Hulting AL. Insulin and leptin levels in patients with schizophrenia or related psychoses: a comparison between different antipsychotic agents. *Psychopharmacology (Berl)* 2001;154: 205–212
- Baptista T, Lacruz A, Hernández L. Why male rats do not gain weight after administration of antipsychotic drugs? Presented at the 31st annual meeting of the Society for Neuroscience; Nov 13, 2001; San Diego, Calif. Session 648.8
- Baptista T, Lacruz A, Acosta A, et al. Naltrexone does not prevent the weight gain and hyperphagia induced by the antipsychotic drug sulpiride in rats. *Appetite* 2000;34:77–86
- Theisen FM, Cichon S, Linden A, et al. Clozapine and weight gain [letter]. *Am J Psychiatry* 2001;158:816
- Wang GJ, Volkow ND, Logan J, et al. Brain dopamine and obesity. *Lancet* 2001;357:354–357
- Steel R, Johnstone EC. Should the treatment of schizophrenia include old antipsychotic drugs? *Curr Psychiatry Rep* 2000;5:404–409
- Mihara K, Kondo T, Suzuki A, et al. Prolactin response to nemonapride, a selective antagonist for D₂ like dopamine receptors, in schizophrenic patients in relation to Taq1A polymorphism of DRD2 gene. *Psychopharmacology (Berl)* 2000;149:246–250
- Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. *J Clin Psychiatry* 2001;62(suppl 7):22–31

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Eosinophilia Associated With Olanzapine

Sir: Clozapine is an effective antipsychotic that is known for its propensity to cause hematological side effects such as agranulocytosis and eosinophilia. The latter is a common side effect during antipsychotic treatment and has been discussed previously as a possible predictor for agranulocytosis.^{1,2} Recent reports indicate that the administration of the novel antipsychotic olanzapine might also be associated with clinically relevant hematological toxicity.^{3–5} Here we report the emergence of eosinophilia in a patient treated with olanzapine for an acute schizomanic episode.

Case report. Mr. A, a 30-year-old white man with a 5-year history of DSM-IV schizoaffective disorder, was hospitalized. He presented with a decreased need to sleep, euphoric mood, increased self-esteem, religious ecstasies, and coenesthesia. Three years earlier, a schizomanic episode had been treated effectively with olanzapine. Medication was continued for 17 months when Mr. A terminated treatment on his own.

At admission, olanzapine treatment in combination with lorazepam, 1.5 mg/day, was started and was gradually increased to 22.5 mg/day. White blood cell (WBC) counts and differential counts were within normal limits before the beginning of treatment. After 5 weeks, the WBC count had increased to $14.9 \times 10^9/L$, of which $7.9 \times 10^9/L$ were eosinophils. Olanzapine treatment was discontinued after consultation with a hematologist, and treatment with perazine was started. A parasitic infection and other causes of eosinophilia were excluded. A blood sample was sent to the Department of Internal Medicine of the Eberhard Karls University, Tübingen, Germany, where a lymphocyte transformation test revealed an enhanced reaction to olanzapine or at least to a component of the tablet. The lymphocyte transformation test has been proven to be helpful for the diagnosis of drug allergy, showing a sensitivity of 78% and a specificity of 85%.⁶ Two weeks after the discontinuation of olanzapine, the WBC count was $8.1 \times 10^9/L$ and the eosinophil count had decreased to 26%. Five weeks after cessation of olanzapine treatment, the WBC count was $8.5 \times 10^9/L$ with 14% eosinophils. Mr. A was discharged 2 weeks later. A control of the hematological parameters 4 weeks after discharge revealed a differential WBC count within normal range.

Eosinophilia can be found in a number of disease processes and occurs as a known side effect during treatment with both conventional and atypical antipsychotic agents.^{2,7} The reported incidence associated with clozapine varies in a range from 0.2% to 64%.^{1,8} Drug-induced eosinophilia might indicate an allergic reaction to the drug⁹ and has been linked to syndromes of significant morbidity and mortality.¹⁰⁻¹² Sometimes it acts as a precursor of neutropenia. Current guidelines from the manufacturer of clozapine recommend discontinuation of the treatment if the eosinophil count is greater than $4.0 \times 10^9/L$.¹³ So far, there are no reports of clinically relevant eosinophilia during olanzapine use. In the present case, the patient developed a leukocytosis paralleled by a significant elevation of the eosinophil count. Since there were no hints for other causes of this finding and the laboratory tests suggested a hypersensitivity to olanzapine or an ingredient of the tablet, it is tentatively concluded that olanzapine has the potential to induce an allergic reaction. Other clinical observations, including hematological studies, are needed to confirm this hypothesis.

REFERENCES

1. Hummer M, Kurz M, Barnas C, et al. Clozapine-induced transient white blood count disorders. *J Clin Psychiatry* 1994;55:429-432
2. Hummer M, Sperner-Unterweger B, Kemmler G, et al. Does eosinophilia predict clozapine induced neutropenia? *Psychopharmacology (Berl)* 1996;124:201-204
3. Felber W, Naumann R, Schuler U, et al. Are there genetic determinants of olanzapine-induced agranulocytosis? *Pharmacopsychiatry* 2000;33:197-198
4. Gajwani P, Tesar GE. Olanzapine-induced neutropenia. *Psychosomatics* 2000;41:150-151
5. Schulz A, Kraus T, Hinze-Selch D, et al. Granulocyte colony-stimulating factor plasma levels during clozapine- and olanzapine-induced granulocytopenia. *Acta Psychiatr Scand* 2000;102:153-155
6. Nyfeler B, Pichler WJ. The lymphocyte transformation test for the

diagnosis of drug allergy: sensitivity and specificity. *Clin Exp Allergy* 1997;27:175-181

7. Ames D, Wirshing WC, Baker RW, et al. Predictive value of eosinophilia for neutropenia during clozapine treatment. *J Clin Psychiatry* 1996;57:579-581
8. Fitton A, Heel RC. Clozapine: a review of its pharmacological properties, and therapeutic use in schizophrenia. *Drugs* 1990;40:722-747
9. Rothenberg ME. Eosinophilia. *N Engl J Med* 1998;338:1592-1600
10. Friedberg JW, Frankenburg FR, Burk J, et al. Clozapine-caused eosinophilic colitis. *Ann Clin Psychiatry* 1995;7:97-98
11. Frankenburg FR, Kando J. Eosinophilia, clozapine, and pancreatitis [letter]. *Lancet* 1992;340:251
12. Amital D, Gross R, Amital H, et al. Coexistence of eosinophilia and agranulocytosis in a clozapine-treated patient [letter]. *Br J Psychiatry* 1997;170:194
13. Clozaril [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2001

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Delusions Associated With Quetiapine-Related Weight Redistribution

Sir: There is established evidence that patients taking conventional antipsychotics tend to exhibit more central obesity than the general population.^{1,2} While there have been numerous case reports focusing on weight gain with novel antipsychotics, there have been no reports of weight redistribution with these medications.³ In the package insert for quetiapine,⁴ the manufacturers report only a 2% incidence in weight gain, and there is no mention of its effects on abdominal adiposity. We report 3 cases in which patients developed delusions associated with an increase in abdominal fat, with virtually no change in overall weight during quetiapine therapy.

Case 1. Mr. A, a 49-year-old Asian American man with chronic paranoid schizophrenia (DSM-IV criteria), was admitted to our hospital for suicidal ideations. Despite medication compliance, which was ensured through weekly visits by a case manager, he experienced only a partial response to atypical antipsychotic medications, including clozapine. At the time of admission, Mr. A had been receiving quetiapine, 700 mg/day, for 1 year and had remained mentally stable, despite a persistent delusion of pregnancy. For 2 years prior to start of quetiapine therapy, he had received olanzapine but experienced no change in weight or body fat distribution. At the time quetiapine was introduced, Mr. A weighed 58 kg (129 lb; body mass index [BMI] = 20 kg/m²) and had a 71-cm waist. After 1 year on quetiapine therapy, his waist size self-reportedly increased to 102 cm (+42%) although his weight remained approximately the same. He subsequently became more preoccupied with his delusion of pregnancy. He often lifted his shirt and rubbed his protuberant abdomen, stating that he was pregnant and could feel the baby kick. His admission was precipitated when he threatened to "remove the baby" with a knife.

All laboratory metabolic parameters were within normal limits, and his diet was controlled during his hospital stay. His suicidal ideations resolved secondary to increasing his quetiapine dosage to 800 mg daily and adding low-dose haloperidol; however, his delusion of pseudocyesis remained persistent, as did his central adiposity.

Case 2. Mr. B, a 41-year-old African American man with chronic paranoid schizophrenia (DSM-IV criteria), was admitted to our facility for increased paranoia and auditory hallucinations. Mr. B had been supervised in regard to the administration of his medications at the board and care facility where he resided. At the time of admission, Mr. B had been receiving quetiapine, 800 mg daily, for 10 months. He recalls his waist size increasing from 91 to 96 cm over this period, although there was little change in his overall weight (103 ± 4 kg [229 ± 9 lb]) over 2 years, BMI = 30 kg/m²). Mr. B complained about the size of his "belly," often grasping his abdominal fat. Mr. B was frequently seen exercising in the common area of the inpatient psychiatric ward and jogging around hospital grounds. He reported that he had been jogging approximately 2.5 miles per day, but it had no impact on his "belly." He suggested that "they" had been putting something into his food at his board and care facility, which resulted in his inability to decrease his waistline despite exercise.

Mr. B was referred to a nutritionist during his admission, and his diet was appropriately adjusted and monitored. In addition, he embarked on an exercise program that failed to demonstrate any change in abdominal girth. Both his glucose and lipid panel levels were borderline high, but did not warrant therapy. Although his auditory hallucinations decreased relative to their frequency and severity at admission, his paranoia in regard to his food being poisoned remained persistent. Eventually, the patient's antipsychotic medication was switched to clozapine, which was effective in decreasing his paranoid delusion. Unfortunately, he was unable to tolerate the sialorrhea that accompanied clozapine treatment, and quetiapine was reinitiated.

Case 3. Mr. C, a 35-year-old white man with chronic paranoid schizophrenia (DSM-IV criteria), was treated with quetiapine, 100 mg at night, for 4 months prior to admission. During this time, his weight decreased from 76 kg (169 lb; BMI = 25 kg/m²) to 73 kg (162 lb; BMI = 24 kg/m²). Nevertheless, he complained of developing an enlarged abdomen and believed he was pregnant with twins. He repeatedly requested to have a urine pregnancy test and an ultrasound to "show the baby" and believed he would "metamorphosize into a woman during the fourth semester." He was discharged on treatment with quetiapine, 300 mg/day; however, he was readmitted 1 month later. He admitted to noncompliance with his medication during this time, and his weight decreased to 70 kg (156 lb; BMI = 23 kg/m²). Quetiapine was reinstated at admission, and despite a slight decrease in overall weight, he continued to complain of an enlarged midsection.

Mr. C had remained compliant with his quetiapine treatment (he was an inpatient for most of this time) with the exception of the month he spent as an outpatient. He was referred to a nutritionist, and his diet was adjusted. His laboratory parameters were within normal limits. Mr. C's quetiapine dosage was slowly titrated up to 600 mg/day, but his delusion failed to respond. Eventually, his antipsychotic medication was switched to risperidone, upon which his abdominal girth lessened, his weight remained steady at 70 kg (156 lb), and his delusion of pregnancy resolved.

There have been rare reports of pseudocyesis in male patients, few of which instances were drug induced.⁵⁻¹¹ Two such cases occurred in association with weight gain and an increase in waist size in the presence of conventional antipsychotics.^{5,8} Our cases suggest that antipsychotic-induced increases in abdominal adiposity can occur independent of weight gain. They also highlight the tendency of psychotic patients to misinterpret anomalous sensory experiences, at times to delusional

intensity. It should be pointed out that all of these patients were chronically ill, had only a partial response to many medications (including clozapine in cases 1 and 2), and had experienced unremitting symptoms despite treatment with quetiapine.

Because antipsychotic pharmacotherapy can result in various iatrogenic sequelae, including weight gain, these cases serve as a reminder for clinicians to carefully inform patients of potential side effects. Although quetiapine minimally affects prolactin levels, patients taking agents that increase prolactin can experience delusional pregnancy when they experience galactorrhea.⁸ Additionally, since diabetes has been shown to be linked with visceral adiposity, these cases suggest that the possible link between new-onset diabetes and novel antipsychotics may be explained by this phenomenon.¹² It seems worthwhile for clinicians to monitor waistlines in addition to weight in patients taking novel antipsychotics to prevent possible iatrogenic complications.

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REFERENCES

1. Stedman T, Welham J. The distribution of adipose tissue in female in-patients receiving psychotropic drugs. *Br J Psychiatry* 1993;162:249-250
2. Haberfellner EM, Rittmannsberger H. Discrepancy between objective weight gain and recognition as a side effect of anti-psychotic treatment [letter]. *Eur Psychiatry* 1999;14:298
3. Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: comparison of weight gain liabilities. *J Clin Psychiatry* 1999;60:358-363
4. Seroquel [package insert]. Wilmington, Del: AstraZeneca Pharmaceuticals LP; 2001
5. Evans DL, Seely TJ. Single case study: pseudocyesis in the male. *J Nerv Ment Dis* 1984;172:37-39
6. Bhat MS, Spear JCM, Robertson PE. Delusions of pregnancy in men. *Br J Psychiatry* 1989;155:423-424
7. Chaturvedi SK. Delusions of pregnancy in men: case report and review of literature. *Br J Psychiatry* 1989;154:716-718
8. Bitton G, Thibaut F, Lefevre-Lesage I. Delusions of pregnancy in a man. *Am J Psychiatry* 1991;148:811-812
9. Miller LJ, Forcier K. Situational influence on the development of delusions of pregnancy in a man [letter]. *Am J Psychiatry* 1992;149:140
10. Shetty MS, Leadbetter RA. Case report: recurrent pseudocyesis in a male patient with psychosis, intermittent hyponatremia, and polydipsia. *Psychosom Med* 1993;55:146-148
11. Silva JA, Leong GB, Ferrari MM. Co-existence of misidentification, pseudocyesis and erotomanic delusions [letter]. *Can J Psychiatry* 1994;39:126
12. Macor C, Ruggeri A, Mazonetto P, et al. Visceral adipose tissue impairs insulin secretion and insulin sensitivity but not energy expenditure in obesity. *Metabolism* 1997;46:123-129

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Switch to Mania After Slow rTMS of the Right Prefrontal Cortex

Sir: Recent evidence indicates that slow repetitive transcranial magnetic stimulation (rTMS) of the right dorsolateral prefrontal cortex (DLPFC) exerts antidepressant effects.¹ Here, we report on 2 patients suffering from a therapy-resistant major depressive episode who had given their written informed consent to participate in a controlled rTMS trial. Both patients underwent 1-Hz rTMS of the right DLPFC and switched from depression to a manic state.

Case 1. A 79-year-old woman, suffering from a recurrent major depressive disorder (DSM-IV) since menopause, underwent 3 adequate antidepressant trials during the current severe depressive episode without clinical improvement. The last medication (20 mg of tranylcypromine, 6 mg of haloperidol, and 0.5 mg of lorazepam) was kept constant for 3 weeks prior to rTMS. The patient underwent 10 rTMS sessions within 2 weeks at the following stimulation parameters: 1 Hz, 110% of motor threshold intensity, 1200 stimuli/day. Scores on the Hamilton Rating Scale for Depression (HAM-D) declined slightly during rTMS (day 0, HAM-D score = 34; day 14, HAM-D score = 29). Lorazepam was discontinued and haloperidol slightly reduced after the last rTMS session. Three days after the last session, the patient developed a severe manic state for 2 days. She became hyperactive, developed a strong appetite, took up smoking, and requested a guitar (Young Mania Rating Scale [YMRS] score = 32). The patient then switched back to a depressive mood and recovered 5 weeks later during valproate and sertraline treatment.

Case 2. A 46-year-old businessman who had been suffering from a pharmacotherapy-resistant severe bipolar I depressive episode (DSM-IV) for 3 years was hospitalized for rTMS and successive ECT. At admission, sertraline, reboxetine, and quetiapine were continued but lamotrigine was stopped in preparation for ECT. Reboxetine was also discontinued due to the patient's severe agitation. Two weeks after admission, the patient underwent 15 rTMS sessions within 3 weeks at the following stimulation parameters: 1 Hz, 110% of motor threshold intensity, 1200 stimuli/day. Depressive symptoms declined (day 0, HAM-D score = 30; day 21, HAM-D score = 16). Mood improvement continued after rTMS, and the patient became manic 7 days after the last session. He dressed fancily, invested thousands of dollars, began to smoke after long abstinence, and became hypersexual (YMRS score = 23). Lamotrigine was started; sertraline was tapered off. After 2 weeks of treatment with quetiapine and lamotrigine without clinical improvement, he received a further 15 sessions of 10-Hz rTMS of the right DLPFC as a putative antimanic treatment.^{2,3} Manic symptoms increased during rTMS, but he recovered with risperidone and valproate treatment.

Switches to mania are frequently seen in bipolar patients during antidepressant pharmacotherapy.⁴ Similarly, 3 cases have been recently reported in patients suffering from a bipolar I or II disorder after fast rTMS of the left DLPFC.^{5,6} Our cases show that manic switches can also occur subsequent to slow (1 Hz) rTMS of the right DLPFC and even in hitherto unipolar depressive patients. However, discontinuation effects, which have been previously reported for lorazepam⁷ and anticonvulsants,⁸ may have contributed to the switches.

In both cases, depressive symptoms remained therapy-resistant during antidepressant pharmacotherapy prior to rTMS, further supporting the possibility of a causal relationship between rTMS and the subsequent switches.

The present cases underline the importance of intensive follow-up after rTMS in patients at risk for bipolar switches. Furthermore the risk of switching should be explained to depressed patients participating in therapeutic rTMS trials.

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REFERENCES

1. Klein E, Kreinin I, Chistyakov A, et al. Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study. *Arch Gen Psychiatry* 1999;56:315-320
2. Grisaru N, Chudakov B, Yaroslavsky Y, et al. Transcranial magnetic stimulation in mania: a controlled study. *Am J Psychiatry* 1998;155:1608-1610
3. Erfurth A, Michael N, Mostert C, et al. Euphoric mania and rapid transcranial magnetic stimulation. *Am J Psychiatry* 2000;157:835-836
4. Himmelhoch JM, Thase ME, Mallinger AG, et al. Tranylcypromine versus imipramine in anergic bipolar depression. *Am J Psychiatry* 1991;148:910-916
5. Dolberg OT, Schreiber S, Grunhaus L. Transcranial magnetic stimulation induced switch into mania: a report of two cases. *Biol Psychiatry* 2001;49:468-470
6. Garcia-Toro M. Acute manic symptomatology during repetitive transcranial magnetic stimulation in a patient with bipolar depression [letter]. *Br J Psychiatry* 1999;175:491
7. Turkington D, Gill P. Mania induced by lorazepam withdrawal: a report of two cases. *J Affect Disord* 1989;17:93-95
8. Scull DA, Trimble MR. Mania precipitated by carbamazepine withdrawal [letter]. *Br J Psychiatry* 1995;167:698

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Exacerbation of Idiopathic Priapism With Risperidone-Citalopram Combination

Sir: Polypharmacy is an increasingly recognized risk factor for unintended medication side effects and adverse events. Recently, a case of priapism attributed to combined treatment with risperidone, olanzapine, and fluvoxamine was described.¹ I report a case of worsening idiopathic priapism while a patient was treated with the antipsychotic risperidone and the selective serotonin reuptake inhibitor citalopram.

Case report. Mr. A, a 29-year-old man from the Congo with never-treated paranoid schizophrenia (DSM-IV), was committed for 6 months to an inpatient unit. He had an excellent response to monotherapy with 4 mg of risperidone daily. A few months into treatment, he developed a severe postpsychotic major depressive episode (DSM-IV) with somatic delusions for which citalopram, 40 mg p.o. q.d., was added to his maintenance risperidone dose of 3 mg daily. About 4 weeks into treatment with the risperidone-citalopram combination, he

mentioned to a nurse that his erections had become longer in duration in the past few weeks, more frequent, and more painful. Upon further questioning, the patient revealed that he had occasionally (about once every 1–2 months) had prolonged erections prior to ever receiving any antipsychotics. The erections would typically wake him up and last up to 4 hours. He had no history of trauma to his genitals. On risperidone treatment alone, he had no clear worsening of this baseline frequency, but the erections were of greater duration, lasting 6 to 8 hours. On treatment with risperidone plus citalopram, he developed almost daily erections of up to 12 hours' duration. Because of Mr. A's good clinical response otherwise, citalopram was decreased to 20 mg p.o. q.d. and risperidone changed to b.i.d. dosing. However, 3 days after the dose adjustments, he experienced an episode of persisting priapism that required urologic emergency intervention with pseudoephedrine and needle detumescence. A sickle cell preparation was normal, and a screening complete blood cell count was within normal limits. Steady-state blood levels for 3 mg of risperidone and 40 mg of citalopram were 15 ng/mL for total risperidone and 64 ng/mL for citalopram. The patient improved after both risperidone and citalopram were discontinued and haloperidol was started. Nevertheless, he continued to have occasional 4-hour erections for several weeks before he was lost to follow-up when he was transferred to another hospital.

Priapism can be idiopathic, or it can be caused by certain medical illnesses and medications.² In this patient, important causes such as sickle cell anemia or malignancy were ruled out. Predisposing factors such as genital trauma or medical medications (e.g., anticoagulants or antihypertensive medications) were not present. Cocaine use, an important condition that can result in priapism,³ was thought to be very unlikely given the locked treatment setting. Priapism can occur during treatment with antipsychotics with affinity for the α_1 -adrenergic receptor. Clozapine, risperidone, and olanzapine all block the α_1 -receptor, and all have been associated with priapism.⁴ However, other neurotransmitter systems are likely contributing or facilitating factors. The serotonin system has been implicated in reports of prolonged erection with fluoxetine⁵ and of priapism with a sertraline-lithium combination.⁶ Citalopram has been implicated in clitoral priapism⁷ but not in male priapism. While it is possible that this patient simply experienced the natural course of idiopathic priapism, the time course of worsening symptoms is consistent with a pharmacodynamic interaction. It is conceivable that only the combined α -adrenergic action from risperidone and the serotonergic action from citalopram (which is virtually devoid of adrenergic antagonism itself⁸) led to full-blown priapism. A pharmacokinetic interaction leading to substantially increased peripheral α -adrenergic activity of risperidone seems unlikely: measured risperidone levels were in the expected low-normal range, consistent with the weak inhibition by citalopram of the cytochrome P450 isoenzymes that metabolize risperidone. However, priapism is not dose related, and the adrenergic antagonism of risperidone alone could have been sufficient.

Patients might not consider long, painful erections abnormal and thus might not volunteer these episodes. It seems prudent to inquire about prolonged erections in all male patients to be treated with psychotropics. This is particularly true if polypharmacy is going to be used, as side effects and adverse events of combined medication regimens are vexingly unpredictable.

Dr. Freudenreich has no affiliation or relationship to report relevant to the subject matter of this letter.

REFERENCES

1. Seger A, Lamberti JS. Priapism associated with polypharmacy [letter]. *J Clin Psychiatry* 2001;62:128
2. Harmon WJ, Nehra A. Priapism: diagnosis and management. *Mayo Clin Proc* 1997;72:350–355
3. Altman AL, Seftel AD, Brown SL, et al. Cocaine associated priapism. *J Urol* 1999;161:1817–1818
4. Compton MT, Miller AH. Priapism associated with conventional and atypical antipsychotic medications: a review. *J Clin Psychiatry* 2001;62:362–366
5. Murray MJ, Hooberman D. Fluoxetine and prolonged erection [letter]. *Am J Psychiatry* 1993;150:167–168
6. Mendelson WB, Franko T. Priapism with sertraline and lithium [letter]. *J Clin Psychopharmacol* 1994;14:434–435
7. Berk M, Acton M. Citalopram-associated clitoral priapism: a case series. *Int Clin Psychopharmacol* 1997;12:121–122
8. Bezchlibnyk-Butler K, Aleksic I, Kennedy SH. Citalopram: a review of pharmacological and clinical effects. *J Psychiatry Neurosci* 2000;25:241–254

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Delirium Caused by Donepezil: A Case Study

Sir: Donepezil, a centrally acting acetylcholinesterase inhibitor, is the first drug introduced in Japan for the symptomatic relief of cognitive impairment in patients with mild-to-moderate Alzheimer's disease. Some authors suggest that cholinomimetic treatment may also benefit certain behavioral problems associated with Alzheimer's disease such as apathy, psychotic symptoms, and agitation.¹ However, several adverse events related to donepezil have been reported so far, the most common being gastrointestinal disturbances due to cholinomimetic effects of donepezil. We herein report on a patient with Alzheimer's disease who presented with delirium during treatment with donepezil.

Case report. Mr. A, a 65-year-old Japanese man with a 6-year history of cognitive impairment, was clinically diagnosed with Alzheimer's disease according to DSM-IV criteria. His Mini-Mental State Examination (MMSE)² score was 16 of 30. There was no history of delirium or behavioral disturbances, and no psychotic phenomena were elicited. Apart from hypertension requiring prescription of nifedipine for about 10 years, Mr. A's medical history was unremarkable. A physical examination showed no abnormalities, including parkinsonism. Results of liver function tests were within normal limits, as were hematologic examination and thyroid function test results and serum ammonia, creatinine, B₁₂, and folate levels. Magnetic resonance brain imaging identified diffuse mild cortical atrophy. He started treatment with 3 mg of donepezil once daily, and after 2 weeks, Mr. A's dose of donepezil was increased to 5 mg/day. No changes were made in the dosages of other drugs (nifedipine, 20 mg/day, for hypertension and sennoside, 24 mg/day, for constipation). Three days later, he became delirious and was subsequently hospitalized owing to agitation and confusion. During the day he showed mild, aimless hyperactivity. He became unable to watch television and could not always recognize family members. He ransacked his room in the ward. He was able to sleep for up to half an hour, but at night he seemed unable to sleep at all and the hyperactivity increased. He went into other patients' rooms and tried to climb into their beds. He

resisted violently every attempt to keep him confined to his quarters. At that point, his MMSE score was 6 of 30. Results of general physical and neurologic examinations were also within normal limits. No evidence of infection was found on either chest X-ray or laboratory studies of blood and urine. He was diagnosed with dementia of the Alzheimer's type with delirium according to DSM-IV criteria. His donepezil treatment was then discontinued immediately. After 2 days, Mr. A was alert and started to recognize family members. He returned to baseline cognitive functioning, but he could not describe the events that led to his admission. He was then discharged to his home. At follow-up 5 months after hospital discharge, his recovery had been maintained.

Although a causal relationship between delirium and donepezil cannot be proved, a temporal relationship between the increase of donepezil and the occurrence of delirium in Mr. A, a patient with no previous history of delirium, warrants caution with the prescription of this drug. In this case, the delirium occurred at the (Japanese) recommended maintenance dose of 5 mg/day of donepezil. There have been few reports of delirium resulting from donepezil administration. Anticholinergic mechanisms underlie numerous common causes of delirium.³ In fact, several authors have suggested that centrally acting acetylcholinesterase inhibitors, including donepezil, improve symptoms of delirium in both Alzheimer's disease^{4,5} and bipolar affective disorder with lithium intoxication.⁶ On the other hand, cholinergic delirium is uncommon. Although it has been reported that another centrally acting cholinesterase inhibitor, tacrine, might induce delirium in patients with Alzheimer's disease,^{7,8} the mechanism of delirium by use of acetylcholinesterase inhibitors is not clear. As donepezil seems a useful drug in some of the carefully selected patients with mild-to-moderate

dementia of the Alzheimer's type, we think that this report will extend our knowledge of the safety profile of donepezil.

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REFERENCES

1. Cummings JL, Kaufer D. Neuropsychiatric aspects of Alzheimer's disease: the cholinergic hypothesis revisited. *Neurology* 1996;47: 876-883
2. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-198
3. Trzepacz PT. Neuropathogenesis of delirium: a need to focus our research. *Psychosomatics* 1994;35:374-391
4. Wengel SP, Roccaforte WH, Burke WJ. Donepezil improves symptoms of delirium in dementia: implications for future research. *J Geriatr Psychiatry Neurol* 1998;11:159-161
5. Wengel SP, Burke WJ, Roccaforte WH. Donepezil for postoperative delirium associated with Alzheimer's disease. *J Am Geriatr Soc* 1999; 47:379-380
6. Fischer P. Successful treatment of nonanticholinergic delirium with a cholinesterase inhibitor [letter]. *J Clin Psychopharmacol* 2001;21:118
7. Hooten WM, Pearlson G. Delirium caused by tacrine and ibuprofen interaction [letter]. *Am J Psychiatry* 1996;153:842
8. Trzepacz PT, Ho V, Mallavarapu H. Cholinergic delirium and neurotoxicity associated with tacrine for Alzheimer's dementia. *Psychosomatics* 1996;37:299-301

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