Letters to the Editor

Sleep-Related Eating Disorder Induced by Risperidone

Sir: We read with great interest the letter by Paquet et al.[1] on sleep-related eating disorder (SRED) induced by olanzapine. The authors presented a case of SRED induced by the addition of olanzapine for the treatment of bipolar I disorder. It is the first case report describing an association between SRED and olanzapine use. Here, we present another case of atypical antipsychotic–induced SRED that was induced by the addition of risperidone for the treatment of psychotic disorder due to vascular dementia. SRED was related to the patient's risperidone dose.

Case report. Mr. A, a 68-year-old man, had DSM-IV–defined psychotic disorder due to vascular dementia. He had no previous history of psychiatric disorder or major systemic disease. Due to profound psychotic symptoms (auditory hallucinations, delusions of persecution, and disorganized behaviors), he visited the psychiatric clinic for evaluation. Results of extensive laboratory tests, including hematologic, serum biochemistry, and urine analyses, were all within normal range. Brain tomography revealed multiple lacunar infarctions over the bilateral frontal area. After 1 month of treatment with risperidone, 1 mg/day, Mr. A's psychotic symptoms persisted and greatly influenced his daily life. His score on the Udvalg for Kliniske Undersøgelser Side Effect Rating Scale (UKU)[2] was 1. After his risperidone dosage was increased to 2 mg/day, his psychotic symptoms gradually resolved.

Mr. A also, however, reported sleep disturbances that began after the increase in risperidone dose and occurred most nights. While asleep, he went to the kitchen, opened the refrigerator, and ate large amounts of food. These episodes were witnessed by his wife, who, when trying to awaken him, was met with an unresponsive reaction. In the morning, the patient had no memory of these episodes. Mr. A's sleep disturbance persisted for 2 months while his risperidone dose remained at 2 mg/day. His score on the UKU increased to 3, with addition of the sleepiness/sedation and weight gain items.

After Mr. A's risperidone dose was reduced to 1 mg/day, these nocturnal eating episodes disappeared rapidly and completely. Brain tomography demonstrated no significant changes compared with previous results. During this period, the patient's concurrent medication included acetylsalicylic acid, 100 mg once daily.

Regarding the chronology of the symptoms, the occurrence of SRED in this case appears clearly related to the addition of risperidone to the patient's treatment. SRED consists of partial arousals from sleep, usually within 2 to 3 hours of sleep onset, ingestion of food in a rapid or "out of control" manner, and subsequent poor memory of the episode.[3]

The underlying pathophysiology of SRED remains unclear. One hypothesis is that an internally generated stimulus (e.g., periodic leg movement, apnea) may produce a partial arousal that, if occurring at the right time (probably non–rapid eye movement sleep) in a predisposed individual, may be associated with a nocturnal eating episode.[3] This mechanism has been proposed as a cause of somnambulism and may similarly produce SRED. These internal stimuli result in arousal that leads to out-of-bed activity. Hypoglycemia or possibly a secondary emotional disorder is hypothesized as the stimulus for eating.[4]

Of note, somnambulism is the predominant disorder responsible for SRED; restless legs syndrome, obstructive sleep apnea, and daytime eating disorder have also been identified as causes.[3,5,6] Somnambulism arises during slow-wave sleep and reflects impairment in the normal mechanism of arousal from sleep, resulting in partial arousal during which motor behaviors are activated without full consciousness.[7] Risperidone, which is known to have potent dopamine D_2 and serotonin 5-HT$_2$ antagonistic properties, has the potential to increase the slow-wave sleep period.[8,9] One study[10] suggested that the decrease in dopaminergic and/or serotonergic activity might contribute to SRED. This phenomenon could explain the dose effect of risperidone-induced SRED observed in our case. The adverse reactions related to risperidone, e.g., akathisia, increase of appetite, and restless legs syndrome,[11] could be partially responsible for the occurrence of SRED by initiating partial arousal. Additionally, dementia is often associated with sleep disturbances, e.g., sleep apnea and restless legs syndrome. Subjects with dementia may be among those at high risk of developing SRED.

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Mong-Liang Lu, M.D., M.S.
Winston W. Shen, M.D.
Taipei Medical University-Wan Fang Hospital
Taipei, Taiwan

Potential for Detection Bias in the Association Between Olanzapine and Diabetes

Sir: In their article on the risk of diabetes during the use of either olanzapine or risperidone, Caro and colleagues[1] found that compared with risperidone, olanzapine was associated with an increased risk of new-onset diabetes. The authors used a retrospective analysis to calculate hazard ratios for the development of diabetes among patients undergoing treatment with olanzapine compared with risperidone.

The authors cited a number of publications over the past 5 years that associate certain atypical agents, especially olanzapine and clozapine, with the development of diabetes. This potential association has been widely commented on in the literature and has been publicized by the manufacturers of competing atypical agents. During recent years, most clinicians prescribing atypical antipsychotics have probably been aware of this possible adverse event. In fact, routine glucose monitoring has been recommended during initiation and maintenance of treatment with olanzapine because of the reported association.

In the dataset Caro et al. studied, 33,946 schizophrenia patients who received at least 1 prescription for either of the 2 atypical agents of interest were identified. The outcome variable was whether or not the patients received a diagnosis of diabetes at a physician visit or had a first medication claim for insulin or an oral hypoglycemic agent. During 18,765 person-years of follow-up, 319 patients developed diabetes after being prescribed olanzapine, compared with 217 patients in the risperidone group over 13,563 person-years of follow-up. Although the overall crude hazard ratio was nonsignificant, after adjustment for age, gender, and haloperidol use, the hazard ratio was 1.30 (CI = 1.05 to 1.65) among women and 1.90 (CI = 1.40 to 2.57) during the first 3 months of treatment among all patients. The authors concluded that olanzapine use was associated with an increased risk of developing diabetes, especially during the first 3 months of treatment, and that it is appropriate to consider periodic glucose monitoring in olanzapine-treated patients.

In the discussion of their findings, the authors noted several important limitations, including (1) the retrospective nature of the study, (2) the use of medication claims data, (3) potential limitations with external validity due to the characteristics of patients included in the dataset, (4) lack of data on patients who may have been admitted to the hospital for the treatment of diabetes, (5) limitations related to the definition of the outcome variable, (6) lack of data on other covariates, and (7) possible inclusion of patients coprescribed other potentially diabetogenic medications. Unfortunately, however, the authors failed to discuss the important potential for misclassification bias (or information bias) in their study.

In general, bias is a systematic error (in contrast to sampling error, which is random) that results in inaccurate estimation of the effect of an exposure on an outcome. Specifically, in the study by Caro and colleagues, effect estimates may have been subject to detection bias. This form of bias results from a systematic error in methods of ascertainment, diagnosis, or verification of cases in an epidemiologic study.[2] Measurement of the outcome of interest (diagnosis of diabetes at a physician visit or a first medication claim for insulin or an oral hypoglycemic agent) may have been systematically inaccurate if physicians were more likely to monitor glucose among olanzapine-treated patients compared with those receiving risperidone. This differential misclassification would have created a bias away from the null hypothesis. A weak observed effect in the presence of a bias away from the null leads to a tenuous argument for a real association. Furthermore, the magnitude of bias is not affected by the large sample size.

At least 2 points support the possibility of the occurrence of detection bias in the effect estimates reported. First, the purported association between olanzapine and diabetes was beginning to be recognized during the study period (1997–1999). A MEDLINE search limited to this time period reveals several published reports of olanzapine-associated hyperglycemia or diabetes,[3–7] and many clinicians were becoming aware of the association during the time frame of the study. A similar MEDLINE search reveals no published cases of risperidone-associated diabetes from 1997 to 1999. Second, it is plausible, because of the emerging knowledge of an olanzapine-diabetes association, that cases of diabetes in the olanzapine group were more readily detected, while potential cases in the risperidone group went undetected, since a risperidone-diabetes association had not yet been reported. In other words, clinicians may have been screening for hyperglycemia among the olanzapine group more readily than among the risperidone group. The findings of the article may not be internally valid due to the potential detection bias that may have occurred. This potential bias should be considered when interpreting the results of the study.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

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Michael T. Compton, M.D., M.P.H.
Emory University School of Medicine
Atlanta, Georgia
Holly A. Hill, M.D., Ph.D.
Rollins School of Public Health of Emory University
Atlanta, Georgia

Dr. Caro Replies

Sir: My colleagues and I believe it is unlikely that detection bias explains our results, given the information available to the prescribers during the time frame of our study (January 1997 to December 1999). During the fourth quarter of 1998, 3 case reports associating olanzapine with diabetes or hyperglycemia were published (2 in October,[1] 1 in December[2]), and in 1999, 4 additional olanzapine cases appeared (in June[3,4] and September[5,6]). Only in fall 1999 was a case series comprising 7 olanzapine cases published.[7] In addition, some cases were reported for other atypical antipsychotic agents; for example, in May 1997, 1 case was reported for risperidone at the American Psychiatric Association annual meeting,[8] and in August 1999, 1 case was also reported for quetiapine.[9] In July 1999, the U.S. Food and Drug Administration indicated their concerns about the number of case reports regarding clozapine and the risk of diabetes.[10] It is possible that the concerns expressed regarding clozapine and diabetes risk could have influenced some prescribers during the second half of 1999, but the information available at the time would have equally increased glucose monitoring for all of the atypical antipsychotic agents, not just olanzapine.

We have repeated the analyses for the period January 1997 to December 1998, i.e., we excluded all of the data collected during 1999. In this reduced dataset, 20,519 patients who received at least 1 prescription for olanzapine or risperidone were identified, with 21,255 person-years of follow-up. After being prescribed olanzapine, 155 patients developed diabetes, and after risperidone, 130 patients developed diabetes. The risk ratio, after adjusting for age, gender, and haloperidol use, was 4.81 (95% CI = 2.99 to 4.72) during the first 3 months of treatment. Early onset of diabetes soon after initiation of treatment is in accord with the published case reports: a recent analysis of 45 published cases showed that 59% of the cases developed within 3 months of commencing treatment with the atypical antipsychotic.[11]

It is also worthy of note that our results are consistent with other recently published retrospective studies using other databases and study designs.[12,13] In addition, studies have since been reported in which researchers reviewed monitored glucose levels and observed greater increases among patients prescribed olanzapine compared with risperidone.[14–16]

On balance, my colleagues and I feel that detection bias should not be seen as a major concern for our study. In combination with the other evidence available, it is very likely that the risk of diabetes with olanzapine is higher than with risperidone. Additional prospective research would be helpful to confirm and quantify the additional risk associated with olanzapine.

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J. Jaime Caro, M.D.C.M.
Caro Research Institute
Concord, Massachusetts

Improvement of Psychosis During Treatment With Estrogen and Progesterone in a Patient With Hypoestrogenemia

Sir: On the basis of clinical evidence and animal studies,[1] estrogen is hypothesized to be a protective factor with regard to illness course in females with schizophrenia.[2] Furthermore, women suffering from schizophrenia have been found to have significantly lower estrogen levels compared with healthy controls.[3] According to these studies, women are more vulnerable with respect to development of psychosis during phases of low estrogen levels such as premenstrual and peripartal states and during discontinuation of oral contraception, as well as in states of primary or secondary hypoestrogenemia.[3,4] We present the case of a patient with psychosis associated with amenorrhea on the basis of hypoestrogenemia whose psychotic symptoms disappeared during treatment with estrogen and progesterone without antipsychotic medication.

Case report. Ms. A, a 23-year-old woman, was admitted to our hospital with florid psychotic symptoms: delusions, thought disorder, and cenesthetic hallucinations, as well as symptoms of derealization. Ms. A's symptoms had persisted for about 4 weeks before her admission to our hospital and fulfilled ICD-10 criteria for a schizophrenic disorder. Her Positive and Negative Syndrome Scale (PANSS)[5] total score was 65 (Figure 1). The patient had to interrupt her education due to her psychotic symptoms.

Figure 1. Positive and Negative Syndrome Scale (PANSS) Scores Before and After Treatment in a Female Schizophrenia Patient
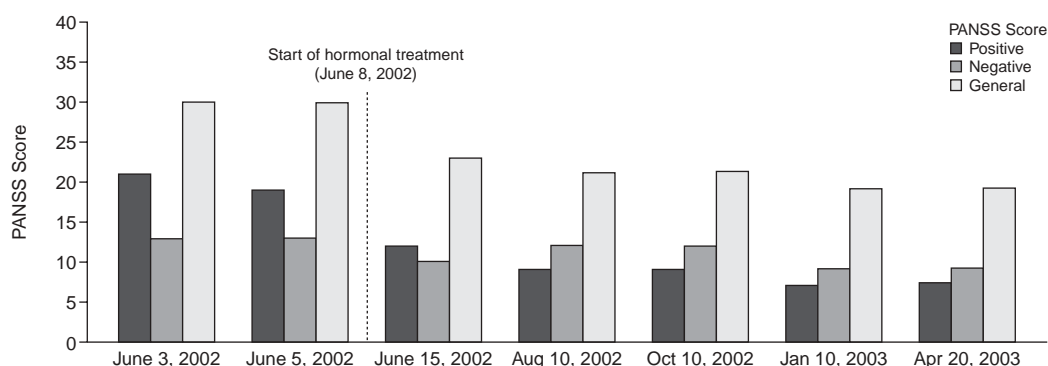
Ms. A had no previous contact with psychiatric institutions and had not used psychotropic medication or other legal or illegal drugs. Results of a drug screen at admission were negative. Her medical history revealed amenorrhea for the 2 years prior to admission. She had experienced menarche at the age of 12 years with irregular menses afterward. Since puberty, she had experienced fluctuating symptoms of derealization, mood swings, and anxiety and reduced interest in studies and social activities, which could be seen as prodromal symptoms. Six years after menarche, Ms. A started taking oral contraceptives, and she reported that psychopathologic symptoms had improved significantly during that period. The patient took oral contraceptives until she was 20 years of age. Her family history showed that both of her sisters suffer from menstrual irregularities with no signs of a psychiatric disorder.

Before starting the current treatment, the patient was examined by a gynecologist. Hormonal analysis was performed and revealed significant hypoestrogenemia (24 ng/L), while levels of the other sexual hormones were within normal range (luteinizing hormone, 3.1 IU/L; follicle-stimulating hormone, 4.7 IU/L; prolactin, 6.1 μg/L; cortisol, 184 μg/L). Consequently, oral contraceptive treatment (11 days of treatment with estradiol valerat, 2 mg/day, followed by 10 days of treatment with estradiol valerat, 2 mg/day, plus norgestrel, 0.5 mg/day) was administered. Each treatment period was followed by 7 days without hormonal medication. About 1 week after Ms. A started hormonal treatment, her psychotic symptoms were found to be substantially improved (PANSS total score of 44) (see Figure 1). After 3 weeks of treatment, all psychotic symptoms had remitted and the patient was discharged. The patient's weekly visits to our outpatient clinic have revealed stable psychopathologic conditions for 10 months (see Figure 1).

To the best of our knowledge, this is the first case of a patient with psychosis and hypoestrogenemia independent of the menstrual cycle, puerperium, or discontinuation of oral contraception whose psychotic symptoms improved with estrogen and progesterone treatment. Symptom remission was achieved with no need for antipsychotic medication.

A PubMed search of publications between 1980 and 2003, using the keywords *schizophrenia* and *sexual hormones*, revealed 71 cases of premenstrual psychosis, 14 cases of menarche-associated psychosis,[6] and 1 report of a woman who experienced a psychotic state after discontinuation of an oral contraceptive and responded to estrogen-gestagen therapy in combination with antipsychotic medication.[7]

Ahokas et al.[8] described 10 patients with puerperal psychosis who stabilized with estrogen treatment. The hypothesis that estrogen has an antipsychotic effect is also supported by Kulkarni et al.,[9] who successfully treated women suffering from schizophrenia with a combination of antipsychotics and estrogen.

These findings are corroborated by animal studies showing that estrogen crosses the blood-brain barrier and modulates several neurotransmitter systems. Estrogen can reduce brain dopamine concentration and influences the sensitivity of, as well as the number of, dopamine receptors in the brain.[3] It is therefore hypothesized to have a protective effect against the development of psychosis.[2] For these reasons, estrogen has been considered an endogenous antipsychotic.

Our patient had most likely experienced prodromal psychotic symptoms since puberty that worsened until manifest psychotic symptoms eventually led to admission. The only time the patient's symptoms improved was during the time she took oral contraceptives, which was why we decided to treat her hypoestrogenemia before starting antipsychotic treatment under inpatient ward conditions. At admission, the patient displayed florid psychotic symptoms that fulfilled ICD-10 criteria for schizophrenia. Psychotic symptoms disappeared when she was treated with estrogen and progesterone, and she showed no side effects caused by hormonal treatment. Generally, potential disadvantages of such a treatment, including a slightly sedating effect of progesterone, should not be neglected.[10] Besides potential benefits, risks of this kind of treatment, such as venous thrombosis and hepatotoxicity, must be considered. A risk of breast cancer has been discussed in respect to hormonal treatment. One investigation suggests a higher risk for the development of breast cancer in women receiving combined estrogen and progesterone therapy as compared with estrogen therapy only,[11] whereas another investigation found no significant effect of the combination therapy on the development of breast cancer.[12]

It could be hypothesized that our patient suffered from a sort of "threshold schizophrenia" that became clinically apparent possibly because of hypoestrogenemia. In conclusion, this case report supports earlier research on the positive influence of estrogen on psychotic symptoms and emphasizes the importance of hormonal screening in the diagnosis of schizophrenia.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

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Maria A. Rettenbacher, M.D.
Sergei Mechtcheriakov, M.D.
Anton Bergant, M.D.
Anita Brugger, M.D.
W. Wolfgang Fleischhacker, M.D.
University Clinics Innsbruck
Innsbruck, Austria

A Case Report of Mania Related to Discontinuation of Bupropion Therapy for Smoking Cessation

Sir: Both initiation and discontinuation of antidepressants are known to induce manic episodes.[1] This side effect must be considered as a severe complication of any antidepressant therapy used in bipolar disorder. It is controversial whether these episodes occur less frequently with newer antidepressants—such as bupropion—than, for example, with classical tricyclic antidepressants.[2,3] Here, we describe the case of a patient who underwent smoking cessation therapy with bupropion, a noradrenergic and dopaminergic reuptake inhibitor, and developed mania 2 weeks after discontinuation.

Case report. Ms. A, a 36-year-old woman, was admitted to the hospital because her relatives were worried about her "unusual behavior." She was convinced that a particular man she knew from long before was communicating with her to express his love. A psychiatric examination revealed racing thoughts, and her speech was circumstantial, in part incomprehensible, and not directed. Her mood was elated and sometimes irritable. She was unusually self-confident, showed psychomotor agita-tion, and reported a decreased need of sleep. These symptoms had developed within a few days and had now lasted for about 2 weeks. Clearly, she was suffering from a manic episode with psychotic features (paranoia erotica). Physical and laboratory investigations were without pathologic findings.

Ms. A's medical history revealed that she had never been treated for any somatic or psychiatric disorder, but she had been nicotine dependent for about 15 years (20–40 cigarettes per day) and consumed alcohol (wine) nearly every day in a dose of 30 to 40 g. However, 3 years previously she had experienced similar manic symptoms for a few days after the breakup of a long-standing partnership, followed soon after by a depressive episode with depressed mood, anhedonia, fatigue, and diminished interest in most activities. This episode remitted after 6 months with no psychiatric treatment. Ms. A had no family history of psychiatric disorder.

Prior to the admission, the patient had been prescribed bupropion by her family doctor to help her stop smoking. She had taken bupropion for 5 weeks in a dose of 300 mg/day. Despite this pharmacologic support, her attempt to stop smoking remained unsuccessful. (She only temporarily reduced her consumption to a minimum of 5 cigarettes/day.) Therefore, she abruptly stopped taking bupropion without consulting her doctor. Two weeks later, Ms. A's first manic symptoms developed. The acute manic episode was treated with 10 mg/day of haloperidol, which was replaced after 5 days by 6 mg/day of risperidone due to severe akathisia. After 16 days, Ms. A's acute manic symptoms were largely remitted and she was discharged. Afterward, she felt "very well," but 3 months later she developed a severe depressive episode that lasted 6 months, interrupted by a 3-week mixed manic episode requiring rehospitalization. Sodium valproate combined with citalopram finally led to full remission.

A clear-cut causal relationship between bupropion discontinuation (and concurrent changes in monoaminergic function) and the patient's manic episode cannot be claimed. However, the proximal onset of manic symptoms suggests this connection. Reduction of nicotine intake during the patient's attempt at cessation could also have played a role. In summary, induction of a manic episode must be considered when treating nicotine dependence in predisposed patients, and full account should be taken of both the medical and the psychiatric history to lower this risk.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

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Nikolaus Michael, M.D.
Andreas Erfurth, M.D.
Volker Arolt, M.D.
Muenster University Hospital
Muenster, Germany

Self-Reported Participation in Nonpharmacologic Treatments for Bipolar Disorder

Sir: Interest in and use of complementary therapies have grown rapidly in recent years[1] despite a lack of controlled research data on safety and efficacy of these treatments. Patients with psychiatric conditions may utilize complementary and alternative therapies at higher rates than those in the general population.[2] Fatigue, headaches, insomnia, depression, and anxiety are the most common reasons cited for seeking alternative treatments.[1,3] In this letter, we report a study of the use of nonpharmacologic treatments, including complementary and alternative therapies, utilized by patients with bipolar disorder.

Method. Data were gathered from July to December 2000 using a survey of common nonpharmacologic treatments, including psychosocial treatments; herbal, mineral, and vitamin supplements; and spiritual and physical approaches (survey available from the authors on request). Additionally, we included approaches that patients report using to help minimize symptoms, including alcohol, illegal drugs, and prayer. Participants were asked to indicate whether they had utilized the approach specifically as treatment for "the symptoms of bipolar disorder." Questions about the outcome, costs, and intensity and duration of participation in each treatment were also included. The surveys were placed in the waiting room of the Bipolar Disorder Clinic and Research Program at the University of Texas Southwestern Medical Center (Dallas, Tex.) and were distributed to patients who had been clinically diagnosed with bipolar disorder by community psychiatrists and other mental health professionals. Patients provided consent, participation was voluntary and anonymous, and no clinical data were collected (i.e., current mood state). The research was approved by the University of Texas Southwestern Institutional Review Board.

Results. A total of 101 surveys were completed. Ninety-seven percent of respondents indicated that they currently received pharmacotherapy for their bipolar illness. The sample was 36% male, and 75% of respondents were recruited from the university-based center. The sample was well educated, with 77% having at least some college education and 25% reporting postgraduate education.

The majority (99%) of respondents had utilized other treatment approaches (mean = 10.2, SD = 7.0) in addition to or instead of pharmacotherapy (Table 1). Most reported multiple activities, with 42% trying between 6 and 10 alternatives to medications. When individual, group, marital, and family psychotherapy was excluded, 38% of the sample had tried at least 1 other nonpharmacologic treatment.

While the questionnaire included items on intensity, duration, and costs associated with each treatment, these items were often skipped by respondents. Due to a large amount of missing data, and concern over a possible response bias, we have not included those findings.

Conclusions. In this pilot investigation, patients with bipolar disorder were using a variety of nonpharmacologic treatments, some commonly endorsed by physicians and others clearly contraindicated for the treatment of bipolar disorder. Use of nonpharmacologic treatments was greater than some reports suggest,[4,5] but consistent with other findings.[6]

It is clear that patients are utilizing complementary treatments to treat symptoms of bipolar disorder. Thorough assessment must include frank queries and disclosure about beliefs in the efficacy of complementary and alternative therapies, as well as other patient-endorsed strategies to manage symptoms. Practitioners and patients should collaborate while developing a treatment plan, so that compatible treatments can be used to optimize clinical outcome.

Table 1. Most Commonly Reported Nonpharmacologic Treatments Used by 101 Bipolar Patients

Treatment Approach	Patients Who Used Treatment (N)	Reduced Symptoms "a Little" or "Somewhat" (%)	Reduced Symptoms "a Lot" or "Completely" (%)
Individual psychotherapy	87	56.3	35.0
Prayer	73	56.0	33.3
Exercise	67	65.6	21.9
Group psychotherapy	58	55.8	21.2
Alcohol	50	35.7	9.5
Avoidance of caffeine	47	68.2	11.4
Miscellaneous therapies[a]	42	62.1	27.0
Meditation	38	76.5	20.6
Relaxation and/or imagery	33	74.2	22.6

[a]Includes art, crystal, music, light, aroma, per, and energy therapies.

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Ellen B. Dennehy, Ph.D.
Robert Gonzalez, M.D.
Trisha Suppes, M.D., Ph.D.
University of Texas Southwestern Medical Center
Dallas, Texas

Modafinil and Antipsychotic-Induced Sedation

Sir: I read with interest the report by Makela et al.[1] in which they describe the successful amelioration of atypical antipsychotic–induced sedation with modafinil in 3 individuals with schizophrenia. They note that modafinil was effective in decreasing hours of sleep without associated worsening of psychosis or other adverse effects. The authors suggest that modafinil "appears to have no significant drug-drug interactions with the atypical antipsychotics."[(p486)] They note: "To our knowledge, these are the first literature reports of the use of modafinil to treat antipsychotic-induced sedation."[(p486)]

In July 2002, I reported a case of modafinil-associated clozapine toxicity wherein treatment of clozapine-induced sedation was accompanied by a doubling of serum clozapine levels and signs of toxicity.[2] It was hypothesized that there was a possible metabolic interaction between modafinil and clozapine, perhaps inhibition of cytochrome P450 2C19 by modafinil, raising serum clozapine levels.

In the first case described by Makela et al., the patient was being treated with modest doses of clozapine (400 mg/day) and experienced no adverse effects from the addition of modafinil to combat sedation. The authors do not, however, report serum clozapine levels either before or after addition of modafinil. It is possible that this patient's serum clozapine level was elevated by modafinil, but because his dose was relatively low, it did not translate into clinical toxicity.

While it is encouraging that these authors were able to use modafinil to effectively combat antipsychotic-induced sedation, a significant problem, the conclusions drawn may not be correct. It is not possible to rule out a metabolic interaction between modafinil and clozapine based on the data Makela et al. present, despite the apparent absence of clinical signs of toxicity. In spite of modafinil's potential for reversing atypical antipsychotic–induced sedation, caution is recommended in coprescription of clozapine and modafinil.

Dr. DeQuardo reports no financial affiliation or other relationship relevant to the subject matter of this letter.

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John R. DeQuardo, M.D.
Colorado Mental Health Institute at Pueblo
Pueblo, Colorado

Dr. Makela Replies

Sir: DeQuardo's[1] July 2002 report is much appreciated. Notably, however, our letter describing 3 cases of modafinil use in treating antipsychotic-induced sedation[2] included only 1 patient receiving clozapine, and the report was prepared and submitted months before the publication of DeQuardo's work. It is sometimes a challenge to expeditiously share valuable information with others in the medical community, given necessary publication time constraints. Aside from this, the question of whether there is a drug-drug interaction between clozapine and modafinil is worthy of further comment.

DeQuardo notes that a significant portion of clozapine is metabolized through cytochrome P450 (CYP) 2C19 and that modafinil inhibits this enzyme. However, other possible routes of degradation of clozapine are via isoenzymes 3A4, 2C9, 2D6, and 1A2. In some patients, these alternative routes may afford adequate metabolism despite any interaction between clozapine and modafinil via 2C19.

The inconsistency in DeQuardo's previous report[1] between "clozapine levels" and the chronology of the modafinil trial is troubling. The report states that the patient had unexpectedly high clozapine levels 3 to 8 weeks after modafinil was discontinued, yet the reference the author uses to support the 2C19 hypothesis states that modafinil is a reversible inhibitor of 2C19.[3] Since modafinil has a half-life of about 12 hours, 3 weeks off

modafinil treatment represents about 60 half-lives, far too long for the 2C19 inhibition to continue and explain the elevated clozapine levels. Lastly, it is disappointing that the serum clozapine levels reported by DeQuardo are the sum of clozapine and norclozapine (the drug and a metabolite formed by several P450 isoenzymes including 2C19, which DeQuardo believes is inhibitory). The better indicator of inhibition via 2C19 would be an increase in serum clozapine concentration, perhaps accompanied by a decrease in norclozapine.

Other literature reports add to the uncertainty of how a clozapine-modafinil interaction could occur. There is in vivo evidence that modafinil induces 3A4/5 activity.[4] Olesen and Linnet[5] studied the relative in vitro contributions of CYP isoforms 1A2, 3A4, 2C9, 2C19, and 2D6 to clozapine N-demethylation using different clozapine concentrations. At relatively low simulated hepatic concentration levels (5 μM), CYP1A2 was the dominant contributor, while CYP3A4 was dominant at higher (50 μM) clozapine concentrations.

These ongoing communications regarding this issue exemplify the importance of reporting clinical observations involving innovative pharmacotherapeutic attempts at optimizing the quality of life in our patients. Regarding modafinil, further comment and discussion regarding its potential use in the treatment of drug-induced and disease state–induced sedation, as well as the reporting of observed potential drug-drug interactions, are encouraged.

Dr. Makela reports no financial affiliation or other relationship relevant to the subject matter of this letter.

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Eugene H. Makela, Pharm.D., B.C.P.P.
West Virginia University
Morgantown, West Virginia

Correction

In the article "Long-Term Antidepressant Efficacy and Safety of Olanzapine/Fluoxetine Combination: A 76-Week Open-Label Study" by Sara A. Corya, M.D., et al. (November 2003 issue, pp. 1349–1356), an error was introduced twice when 5.6 (SD = 6.6) kg was converted to pounds.

The corrected weight conversion to pounds is 12.3 (SD = 14.5) lb in the "Results" section on page 1352, right column, 5 lines from the bottom, and in the "Discussion" section on page 1355, left column, second paragraph, first sentence. The online version has been corrected.

The staff regrets the error.