

## A Systematic Review of Research on Strategies for the Management of Antipsychotic-Induced Sexual Dysfunction: High-Level Evidence Is Needed

**Sir:** The use of antipsychotic drugs is frequently associated with sexual dysfunction. Symptoms may concern penile erection, lubrication, orgasm, libido, sexual arousal, or overall sexual satisfaction. Different strategies to treat antipsychotic-induced sexual dysfunction have been developed, including drug holidays, dose reduction, switching to another drug, and use of a number of agents for symptomatic therapy. Within the framework of systematic review for the Cochrane Collaboration,<sup>1</sup> our objective was to review the effectiveness of these strategies for the treatment of antipsychotic-induced sexual dysfunction.

**Data Sources and Study Selection.** The trial register of the Cochrane Schizophrenia Group, the Cochrane Central Register of Controlled Trials, EMBASE, MEDLINE, and the PsycLIT databases were searched for relevant trials reported through August 2005 using sexual dysfunction symptoms and antipsychotic terms as keywords (see reference 2 for specific terms). First only randomized controlled trials were searched, and then the search was expanded to all available evidence regardless of level of evidence. The first author of each study was contacted for additional references and for any unpublished trials or data, and the reference lists of all identified studies were inspected for additional studies. Companies involved in production of the principal antipsychotics who offer a drug information service and those involved in the production of the possible agents for symptomatic therapy were also contacted to request additional studies. Study selection, data extraction, and assessment of methodological quality (using a classification recommended by the Cochrane Library<sup>2</sup>) were performed independently by 2 reviewers (M.M.B. and M.H.).

**Data Synthesis.** Two randomized controlled trials concerning symptomatic drug therapy of antipsychotic-induced sexual dysfunction were identified.<sup>3,4</sup> In one of them<sup>3</sup> (N = 10, crossover), no evidence was found for the effectiveness of selegiline (15 mg) in improving sexual functioning in schizophrenic patients maintained on neuroleptic treatment. Another crossover trial<sup>4</sup> evaluating the administration of sildenafil (flexible doses of 25–50 mg; N = 32) found positive effects in all examined outcomes: number of erections sufficient for penetration, mean duration of erections, frequency of satisfactory intercourse, and satisfaction with treatment.

Two open-label trials (N = 10,<sup>5</sup> N = 12<sup>6</sup>) and 2 case reports<sup>7,8</sup> (each with N = 1) also support the effectiveness of sildenafil at doses of 25 to 100 mg in patients with schizophrenia and schizoaffective disorder. One observational study<sup>9</sup> (N = 8) describes the effectiveness of 25 to 50 mg of imipramine as add-on therapy in patients with schizophrenia. Two other open-label studies (N = 10,<sup>10</sup> N = 12<sup>11</sup>) provide evidence for 100 to 300 mg of amantadine as additional medication in patients with schizophrenia. Observational (N = 8 to 20) and case report (N = 1 to 5) evidence was found for the effectiveness of switching to another antipsychotic medication (e.g., quetiapine, olanzapine) as a strategy for dealing with sexual adverse effects of antipsychotic treatment.<sup>12–17</sup> For dose reduction and drug holidays as management strategies, no evaluation data could be identified.

Sexual dysfunction as a side effect of antipsychotic medication might have a great impact on quality of life and antipsy-

chotic treatment compliance.<sup>18–21</sup> Although some observational studies and case reports recommend possibly effective strategies, to date high-level evidence for use of an additional medication exists only for sildenafil. Further randomized controlled trials are needed.

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### Mixed Depression, Suicidality, and Antidepressants

**Sir:** The important article by Bauer et al.<sup>1</sup> showed no association between antidepressants and suicidality in bipolar depression. However, among the correlates of suicidality, intradepression manic symptoms at intake, before antidepressant treatment was started, increased the odds ratio of suicidality to 1.62. The article seems to underplay this important finding, given the recent warning of the U.S. Food and Drug Administration (FDA)<sup>2</sup> about the need to monitor patients during antidepressant treatment for the emergence of possible precursors to suicidality, including manic symptoms such as irritability and psychomotor agitation, which are common intradepression manic symptoms.

In a previous article,<sup>3</sup> Bauer et al. reported that 70% of bipolar patients in a depressive episode had 2 or more intradepression manic symptoms. Recent studies (references 4–16, to list a few) have shown that noneuphoric intradepression manic/hypomanic symptoms (i.e., mixed depression, depressive mixed states) are common in DSM-IV bipolar I, bipolar II, and major depressive disorder depressions. The most common DSM-IV intradepression manic/hypomanic symptoms are irritability, racing/crowded thoughts, psychomotor agitation, and talkativeness.

Related to the FDA's linking of antidepressants to possible precursors of suicidality, another series of recent cross-sectional studies has shown associations between racing/crowded thoughts and suicidality and between psychomotor agitation and suicidality.<sup>9,17–21</sup> However, cross-sectional studies cannot show the direction of a causal relationship, if there is any. The prospective study by Bauer et al.<sup>1</sup> has shown the direction of this possible causal association for suicidality related to antidepressants (i.e., mixed depression may be a possible precursor to suicidality). Furthermore, a newly published study<sup>22</sup> has shown that mixed depression was frequently present just before a suicide attempt. Preliminary analysis of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) database<sup>23</sup> and another study<sup>24</sup> have shown that antidepressants may worsen intradepression manic/hypomanic symptoms.

The logical conclusion on the basis of all the above studies (only some of which are reported due to space limitations) is that mixed depression should be carefully assessed by clinicians, that some symptoms of mixed depression may increase the risk of suicidality (especially psychomotor agitation and racing/crowded thoughts), and that antidepressants can worsen intradepression manic/hypomanic symptoms. This worsening of manic/hypomanic symptoms may be the way by which some mixed depressed individuals treated with antidepressants alone (i.e., no concurrent mood-stabilizing agents) show an increase in or new onset of suicidality.<sup>25,26</sup>

Bauer and colleagues' recent article could be more useful to clinicians not only by reassuring them about the low risk of

antidepressant-induced suicidality, but also by emphasizing that suicidality may follow mixed depression, that mixed depression is common, and that it has been observed that antidepressants may worsen mixed depression and in this way increase or induce suicidality in some individuals. Mood-stabilizing agents would be required to control intradepression manic symptoms before starting antidepressant treatment in mixed depression.

*Dr. Benazzi reports no financial or other relationship relevant to the subject of this letter.*

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### Dr. Bauer Replies

**Sir:** Dr. Benazzi's scholarly letter regarding our recent report that antidepressants do not increase suicidality in individuals with bipolar disorder amplifies a point that we reported but did not extensively discuss: that manic symptoms are associated with increased rates of suicidality. Our finding that such symptoms do not mediate antidepressant effects does not mean that these symptoms are not of impact in their own right. On the contrary, manic symptoms are common during bipolar depressive episodes, as Dr. Benazzi's extensive review points out. He further correctly notes that their presence during bipolar depression heralds poor outcome.

Dr. Benazzi cites our most recent study on the prevalence of manic and depressive symptoms in an unselected health maintenance organization (HMO) population.<sup>1</sup> We reported that the most common mood state of individuals with bipolar disorder was neither mania nor depression, but rather an admixture of both types of symptoms. We speculated that the presence of manic symptoms may be partially responsible for the abysmally low response rates to antidepressants in bipolar depression.

I have argued in one of the major textbooks of psychiatry<sup>2</sup> that to label this disorder *bipolar* is actually misleading. The reason is 2-fold. First, evidence indicates that pure polar states occur in only a minority of cases. Second, the bulk of the social morbidity of the disorder is driven by the depressive phase of the illness, which, as Dr. Benazzi reminds us, is typically mixed. Current trends to the contrary, I proposed a return to the term *manic-depressive* as a more accurate name for the disorder. Accordingly, the editors of the textbook accepted a dual title for the chapter, "Bipolar (Manic-Depressive) Disorders."

We appreciate Dr. Benazzi's highlighting the issue of mixed symptomatology in bipolar disorder and hope that both language and data keep the field focused on this important issue.

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*Dr. Bauer reports no additional financial or other relationship relevant to the subject of this letter.*

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### Long-Acting Injectable Risperidone for Control of Agitation in Dementia

**Sir:** There are now many studies showing the effectiveness of risperidone in controlling agitation in patients with dementia, and it has a relatively benign adverse effect profile. Atypical antipsychotic agents are moderately effective in the treatment of behavioral symptoms in patients with dementia.<sup>1</sup> Failure to adhere to a prescribed medication regimen by patients with psychosis is one of the most frustrating problems faced by mental health care providers, because of the high risk of relapse associated with that situation. For patients with psychosis who will not or cannot take oral medications on a regular daily basis or who have other characteristics, such as memory, visual, or auditory impairment, that contribute to partial compliance, long-acting injectable antipsychotic medication offers a good solution.<sup>2</sup>

Atypical antipsychotics in particular are increasingly being used in many different disorders beyond psychosis in the psychiatric patient population. Dementia with psychotic features is one of those disorders, but depot or long-acting atypical antipsychotic usage has not yet been reported. There are few studies regarding the use of depot antipsychotics in elderly patients. Long-acting injectable risperidone was associated with significant symptom improvement in treatment-stable elderly patients with schizophrenia or schizoaffective disorder.<sup>3</sup> However, to our knowledge, treatment of dementia with long-acting injectable risperidone has not been reported. We report the case of a woman who had developed abnormal behavior due to dementia and was successfully treated with long-acting injectable risperidone.

**Case report.** Ms. A, a 70-year-old woman, was admitted to the outpatient psychiatry clinic of Gaziantep University Hospital (Gaziantep, Turkey) in February 2005 with abnormal behaviors and agitation for 1 week and a 4-year history of dementia symptoms. The age at onset, nonexistence of any other systemic disorder, slow development of disturbance of orientation, and the illness features of psychotic content, steady state of clinical presentation (worsening during a 4-year period), and nonexistence of disturbance in consciousness were the discrimination points of dementia from any form of psychotic disorder or delirious state. Ms. A was a widow and had 5 children who were poorly educated. Her daughter had an anxiety disorder that was stable with treatment, and her other 4 children had no psychiatric disorder. She lived with her daughter in the city center. Her socioeconomic state was moderate. Her relatives gave no history of psychiatric or personality disorder in her premorbid life before the dementia symptoms began.

In Ms. A's mental state examination, disruption of recall of previous events, agnosia to things of daily use (disturbance of defining door, chair, and pencil, etc.), and word and sentence repeat failure were noted, and she was also unable to define abstract proverbs. In addition, she exhibited abnormal behaviors

**Table 1. Scores at Baseline and 1, 2, and 3 Months on the Pittsburgh Agitation Scale (PAS) and Extrapyramidal Symptom Rating Scale (ESRS)**

Scale	Baseline	1 Month	2 Months	3 Months
PAS	14	8	4	0
ESRS	0	0	0	0

(i.e., defecation in rooms) and agitation (i.e., hitting children, shouting, throwing things). Ms. A's Mini-Mental State Examination<sup>4</sup> score was 6, and her Pittsburgh Agitation Scale (PAS)<sup>5</sup> score was 14. Findings of neurologic and laboratory examinations (including imaging) were within normal range. On the basis of these findings, other types of dementia were ruled out, and Ms. A's diagnosis became definite. She was diagnosed as having Alzheimer's type dementia with behavioral disturbance according to DSM-IV criteria.<sup>6</sup>

The patient had taken 2 mg/day of risperidone orally for 7 days on an irregular basis. On the third day after admission (tenth day of risperidone treatment), we added long-acting injectable risperidone 25 mg to the patient's risperidone solution 2-mg/day regimen because of the patient's noncompliance (due to her difficulty with taking oral medication) and in order to begin treatment immediately. Because of the effectiveness and nonexistence of side effects seen with this drug according to Ms. A's medical history, risperidone treatment was maintained. Gradual clinical improvement in agitation, abnormal behaviors, and psychotic symptoms began after a 3-week interval. Because of the possible effectiveness of the depot formulation, and because of the patient's noncompliance with oral intake, treatment with oral medication was stopped in its third week. Injections were administered at 25 mg every 2 weeks for 3 months. The patient's daughter, who was her caregiver, was well informed about the course of illness, and outpatient visits also included supportive therapy for the patient's relatives.

The PAS and Extrapyramidal Symptom Rating Scale (ESRS)<sup>7</sup> were administered to the patient at every visit. Scale scores at baseline and at 1, 2, and 3 months are presented in Table 1. Significant changes from baseline in PAS scores, which included agitation and abnormal behavior improvement, were seen as early as the first month and continued through the third month. No changes from baseline in ESRS scores were seen in any category, because no extrapyramidal symptoms developed in the patient.

Risperidone is a benzisoxazole derivative that has proven efficacy against the positive and negative symptoms of schizophrenia. It has recently been investigated and shown efficacy as a treatment for the behavioral and psychological symptoms associated with dementia in the elderly.<sup>8</sup> Although low risks of cerebrovascular accident and stroke and low mortality rates were found with risperidone,<sup>9-11</sup> caution may be advisable when it is used in older patients.<sup>12</sup> There are few studies regarding the use of depot antipsychotics in elderly patients, especially patients with dementia. We note that fluctuations in dementia-related psychotic and behavioral symptoms would suggest not using depot antipsychotics. However, our patient's psychotic symptoms were stable, and she was an end-stage dementia patient; therefore, we chose to administer a long-acting antipsychotic drug. Available studies indicate that traditional antipsychotic agents given as depot injections are associated with positive outcomes in the elderly.<sup>2</sup> Because the risks for extrapyramidal symptoms and tardive dyskinesia are reduced dramatically with atypical antipsychotics compared with traditional agents and other depot formulations, the development of long-acting atypi-

cal antipsychotic formulations has been pursued. Of the atypical antipsychotics, risperidone is the first agent to be approved in a long-acting injectable formulation.<sup>2</sup>

In addition to reducing psychotic symptoms, long-acting injectable risperidone significantly reduced the severity of behavioral symptoms and agitation in a noncompliant patient with dementia.

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

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## Association Between Clozapine-Induced Agranulocytosis and HLA Subtyping

**Sir:** Clozapine has been shown to be more effective than other antipsychotic drugs in the treatment of schizophrenia.<sup>1</sup> Clozapine is a low-potency compound that has preferential antagonist activity at 5-HT<sub>2</sub> receptors, followed by activity at adrenergic, cholinergic, and histamine receptors and only modest activity at D<sub>1</sub> and D<sub>2</sub> receptors. Despite its superior clinical pro-

**Table 1. HLA Subtyping of a Patient With Clozapine-Induced Agranulocytosis**

Low-Resolution PCR DR	High-Resolution PCR DR	High-Resolution PCR DQA	High-Resolution PCR DQB
DRB1*07	DRB1*0701	DQA1*0102 <sup>a</sup>	DQB1*0202
DRB1*15	DRB1*1501	DQA1*0201	DQB1*0602

<sup>a</sup>Associated with clozapine-induced agranulocytosis.

Abbreviations: HLA = human leukocyte antigen, PCR = polymerase chain reaction.

file, the use of clozapine is limited by the risk of serious and potentially life-threatening side effects, such as leukopenia and agranulocytosis. The incidence of clozapine-induced agranulocytosis has consistently been estimated to be about 0.8% at 1 year,<sup>2-4</sup> and the incidence of neutropenia has been reported to vary from 2.3%<sup>3</sup> to 22%<sup>5</sup> at 1 year.

Different mechanisms for the hematologic complications of clozapine have been proposed, although it is unclear whether the cytotoxic effect is immune mediated or caused by toxicity of the drug or its metabolites.<sup>6</sup> Several phenotypes of the human leukocyte antigen (HLA) system have been associated with clozapine-induced adverse reactions in previous reports. Specifically, some HLA haplotypes have been described as more prevalent in clozapine-induced agranulocytosis in Caucasians: HLA-DR\*02,<sup>7</sup> DRB1\*1601,<sup>7</sup> DRB3\*0202,<sup>8</sup> DRB5\*02,<sup>7</sup> DQA1\*0102,<sup>8</sup> and DQB1\*0502.<sup>7</sup> On the other hand, some HLA haplotypes, such as HLA-B35, have been reported as protective from agranulocytosis.<sup>7</sup>

We present the case of a patient with schizophrenia who developed clozapine-induced agranulocytosis and in whom HLA haplotype analyses were performed to determine whether the agranulocytosis was associated with the described risk haplotypes.

**Case report.** Mr. A, a 53-year-old Caucasian man, was diagnosed with schizotypal disorder (ICD-10: F21) 20 years ago. The illness course had been unstable, with several relapses and admissions to psychiatric units. He had been treated with several antipsychotics including conventional and atypical agents, with partial response. When Mr. A was admitted into the psychiatric unit in January 2005, his symptoms consisted of paranoid delusions and disorganized and aggressive behavior.

Three months earlier, clozapine treatment had been started and titrated to 300 mg/day, with weekly complete blood cell (CBC) counts within normal range. Thirteen days after his admission, he developed fever, cough, purulent sputum, rest dyspnea, and orthopnea and was diagnosed with bronchiolitis obliterans with organizing pneumonia. CBC counts showed leukopenia with neutropenia. A bone marrow aspiration study showed agranulocytosis. Mr. A had to remain isolated in a special unit with ventilatory support.

Clozapine treatment was interrupted, and empirical antibiotic treatment with piperacillin, tazobactam, amikacin, and amphotericin was initiated. Granulocyte-colony stimulating factor treatment was also initiated at 5 mg/kg/day. The patient's fever, agranulocytosis, and toxic hepatitis remained for 15 days, after which the granulocyte-colony stimulating factor dose was augmented to 10 mg/kg/day and the patient reached clinical and analytical recovery. An HLA haplotype study was performed (Table 1) that showed one of the phenotypes previously associated with risk of agranulocytosis: HLA-DQA1\*0102.

Early detection of risk markers of agranulocytosis in candidates for clozapine treatment may help to identify those patients who could potentially develop fatal complications. In view of the severity of clozapine-induced hematologic side effects, HLA haplotyping should be recommended prior to initiation of a clozapine regimen.

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