Toxic Catatonia Secondary to Azithromycin

Sir: Several publications report psychiatric symptoms induced by macrolide antibiotics. Clarithromycin and erythromycin used in combination with other treatments, or even in monotherapy, have been reported to produce acute psychoses,[1–6] manic episodes,[7–12] and depression.[13] To our knowledge, this is the first report of an association between azithromycin, another macrolide antibiotic, and the initiation of acute psychotic depression with catatonic symptoms.

Case report. Ms. A, an 81-year-old woman with a history of hypertension treated with spironolactone and chlortalidone and eyelid carcinoma treated with surgery and radiotherapy 1 year ago, had no known neurologic or psychiatric disorder except for a mourning reaction to the death of her son 15 years ago. Two weeks before admission to our hospital, she developed a flu syndrome that included myalgias, cough, and fever. The primary care doctor gave her amoxicillin, which led to the disappearance of all symptoms except tracheobronchitis.

After 8 days, her doctor stopped amoxicillin treatment and began treatment with azithromycin 500 mg/day for 3 days. Before starting azithromycin, Ms. A was psychiatrically well. After the third day of azithromycin treatment, she presented with progressive psychomotor inhibition, insomnia, anorexia, and depressive cognitions about incurability and hopelessness. The next day, she had catastrophic and nihilistic delusions ("My family has gone far away," "We don't have money and anything to eat," "We don't have a house") with suicidal ideation. She was prescribed venlafaxine 75 mg/day, but she refused medication and food intake.

She was admitted to our emergency department, where she showed good orientation with regard to time and place. However, it was difficult to complete the Mini-Mental State Examination[14] because of psychomotor inhibition that included brief speech and increased latency of response. The patient also showed depressive cognitions with delusional thoughts. Sometimes she became mute and assumed antigravitatory postures. She scored positive on 8 (immobility/stupor, staring, posturing/catalepsy, grimacing, rigidity, negativism, waxy flexibility, withdrawal) of the 14 first items on the Bush-Francis Catatonia Rating Scale.[15] Physical and neurologic examinations, laboratory tests (white blood cell count = 12,000/μL: 86% neutrophils, 6% lymphocytes, 6% monocytes; platelet count = 261,000 mm^3; red blood cells 4,570,000 mm^3; alanine aminotransferase 51 IU/L; γ-glutamyltransferase 3 IU/L; bilirubin 1.1 mg/dL; alkaline phosphatase 187 IU/L; creatine kinase 250 IU/;, creatine phosphokinase 15 IU/L; calcium 9.4 mg/dL), urine test, thyroid levels, toxicology, computed tomography scan of the brain, and lumbar puncture were unremarkable.

She was admitted to the psychiatry inpatient unit with the diagnosis of DSM-IV-TR major depressive disorder (F33.3) with psychotic and catatonic features. We stopped azithromycin, continued venlafaxine 150 mg/day, and added lorazepam 3 mg/day. One day later, we started electroconvulsive therapy (ECT) because the catatonic symptoms as well as the refusal of food and drink intake persisted. After 9 sessions of ECT, a fast, progressive, and complete remission of the symptomatology was observed. ECT stimuli were delivered by means of a MECTA model Spectrum 5000Q device (MECTA Corp., Tualatlin, Ore.) with a standard bifrontotemporal placement and electroencephalogram (EEG) record with cutaneous leads placed in positions FP1, FP2 (10-20 International Federation System), and between the 2 positions. The magnitude of the electrical stimulus was as follows: current, 0.8 A; frequency, 80 Hz; pulse width, 1.8 ms; duration, 2 s. The total EEG convulsion was 203 seconds. Venlafaxine and lorazepam were stopped after a few weeks, and the patient remained asymptomatic 1 year later.

Given the close temporal relationship between treatment with azithromycin and the development of catatonic symptoms, and given that the patient had no history of psychiatric disorders, we believe that this case of acute psychotic depression with catatonic symptoms was most likely induced by the use of azithromycin. Although medication and ECT were introduced, the patient's rapid and complete remission and the fact that the patient remained depression free at 1 year despite having received antidepressant medication for only a few weeks strengthens the case that the psychiatric illness was drug-induced.[16]

The mechanism by which macrolides lead to acute psychiatric episodes is unknown.[1] This family of antibiotics, especially erythromycin and clarithromycin, produces an inhibition of the hepatic cytochrome P450 (CYP) isoenzymes, subclass CYP3A4.[17] Finkenbine and Frye[2] reported a case of psychosis induced by the interaction of clarithromycin and exogenous prednisone, and explained that this symptomatology was due to elevated plasma levels of unmetabolized prednisone. Neff and Kuo[10] described a case of clarithromycin-induced mania in a patient treated with amitriptyline that was a result of high levels of this antidepressant due to cytochrome P450 isoenzyme inhibition. Pollak and colleagues[3] reported a case of delirium secondary to the addition of clarithromycin in a patient who was treated with fluoxetine, hypothetically causing an increase of this antidepressant's level. There are many reviews about clarithromycin- and erythromycin-induced drug interactions with psychotropic agents. Azithromycin, however, has been shown to have little interaction with the cytochrome P450 system and has good tolerability as well.[17] It is more difficult to know how these antibiotics can induce psychiatric symptoms in monotherapy; for this reason, an idiosyncratic reaction could be the explanation for these cases.

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Maria Teresa Plana, M.D.
Jordi Blanch, M.D., Ph.D.
Soledad Romero, M.D.
Montserrat Serra, M.D.
Cristobal Gasto, M.D., Ph.D.
Clinical Institute of Neurosciences
Hospital Clinic, University of Barcelona
Barcelona, Spain

3-Acetyl-7-Oxo-Dehydroepiandrosterone for Healing Treatment-Resistant Posttraumatic Stress Disorder in Women: 5 Case Reports

Sir: Chronic severe posttraumatic stress disorder (PTSD) resulting from early physical and/or sexual abuse is a highly prevalent psychiatric condition in women. PTSD causes persistent functional impairment and emotional distress and generally shows only a limited response to current available psychopharmacologic treatments. Selective serotonin reuptake inhibitors (SSRIs), the most commonly used and only U.S. Food and Drug Administration–approved treatment for this condition, have shown a modest treatment effect of between 0.3 and 0.5.[1–3] Consequently, many of these patients remain quite ill and impaired in their functioning, even after numerous trials and years on medication treatment.

The following case reports are of 5 women with severe chronic PTSD resulting from severe early abuse who continued to be highly symptomatic despite receiving extensive psychotherapy and years of psychopharmacologic treatment. All 5 of these treatment-resistant patients experienced a rapid and substantial reduction in their trauma and affective symptoms after starting on treatment with 3-acetyl-7-oxo-dehydroepiandrosterone, which is a metabolite of dehydroepiandrosterone (DHEA) and is also known as 7-keto DHEA. The improvements in these symptoms not only were subjective and objective, but also manifested in significant and rapid benefits in vocational and interpersonal functioning.

7-Keto DHEA was chosen because (as described in detail in the discussion) it appears to be have benefits as a natural antiglucocorticoid similar to or perhaps even greater than those of DHEA—which has been shown in numerous studies to be beneficial for memory, cognition, depression, dysthymia, sexual functioning, anxiety, and dissociation—but without the hazards of aromatization to testosterone or estrogen found with DHEA. As with DHEA, the exact mechanism of action of 7-keto DHEA is not known, but a putative mechanism is that it may in humans, as in mice, confer neuroprotection and prevent corticosterone-induced neuronal damage. DHEA sulfate levels were measured before treatment since low levels, as described below, are known to correlate with a less resilient response to stress, and the fact that the patients had low levels provided more justification for a treatment that might help reduce their dissociation and dysfunctional responses to stress.

Case 1. Ms. A, a 43-year-old woman with chronic severe PTSD associated with a history of severe physical and sexual abuse beginning in childhood (age 4), had remained highly symptomatic despite individual and group cognitive-behavioral therapy (CBT) for 4 and a half years and trials of fluoxetine 60 mg/day, to which bupropion 150 mg/day and then sertraline 100 mg/day were added. She did not respond to prior trials of olanzapine, quetiapine, or venlafaxine and could not tolerate mirtazapine.

Ms. A had comorbid diagnoses of DSM-IV bipolar II disorder and dissociative identity disorder as well as hepatitis C virus and type 1 (insulin-dependent) diabetes mellitus. Prior to starting on 7-keto DHEA treatment, her DHEAS level was 70 μg/dL (in the lowest quartile of the normal range of 32–240 μg/dL).

Her symptoms included hypervigilance, constant anxiety, fearfulness, flashbacks, frequent dissociative experiences, affective lability, decreased libido, irritability, avoidance, numbing, and frequent inability to "feel" her feelings. Ms. A's dissociative symptoms, fearfulness, and mental anguish were so severe that several other patients in the trauma program were worried about her and came to one of the authors (S.S.) asking her to help Ms. A.

That author had worked with Ms. A for 4 years prior to starting her on treatment with 7-keto DHEA but was unable to develop a good therapeutic relationship because Ms. A was so fearful and avoidant she would miss many sessions, and she was so fragile and frightened she would frequently dissociate during sessions and forget what had been talked about. This all changed within the first week of starting on 7-keto DHEA 25 mg/day in 2005: Ms. A stopped feeling so fearful, stopped dissociating, was much more communicative, and related better. She reported feeling "more organized, more present" and being able to enjoy socializing "with a significant lessening of constant fear and self-criticism."

Anxiety and feelings of detachment, though markedly diminished, were still present, so her dosage of 7-keto DHEA was increased to 50 mg daily. Ms. A described even further improvement after this dosage increase. She said this dosage gave her even more mental clarity and energy as well as better memory and allowed her to feel "more centered" and able to "feel my feelings" without dissociating. After 3 weeks on a 50-mg/day dose, she said, "I am more aware and accepting of my own and other people's issues. It's like I was sleeping and I woke up." She stopped having nightmares, had much better concentration, functioned better at work and in social situations, had more stable mood (she said that "the high is not so high and the low is not so low"), and for the first time was able to handle stressful situations constructively and independently. She said she went from having no libido to some libido and was now interested in dating, after years of avoiding men. Ms. A now has an excellent therapeutic relationship with her psychiatrist, no longer avoids

treatment, and recently said, "This is the first time I realize why people want to be alive."

Case 2. Ms. B, a 55-year-old woman with chronic severe PTSD (DSM-IV) associated with a history of severe childhood physical and sexual abuse, had remained highly symptomatic despite undergoing 1 and a half years of individual and group CBT and receiving paroxetine up to 30 mg daily, from other practitioners, for more than 4 years. She had a history of failed trials on fluoxetine and sertraline; both drugs caused her to be agitated and irritable. She wished to be tapered off paroxetine because she had gained 40 lb on it, and after becoming obese, she also became hypertensive. Ms. B also said she felt that paroxetine was not helping her chronic severe anxiety and irritability. Although her paroxetine dosage was tapered to 5 mg every other day and lamotrigine 100 mg and topiramate 75 mg daily were added by one of the authors (S.S.), she remained highly symptomatic.

Prior to starting on 7-keto DHEA in 2005, Ms. B had severe mood lability, alternating between irritability and fearfulness; was chronically anxious and depressed; and reported feeling helpless and "alone." She was fired from her last job due to nonattendance and was too agitated, irritable, and labile to function at any job. She had frequent flashbacks of childhood physical abuse and intrusive thoughts regarding sexual abuse. Ms. B's other symptoms of PTSD included avoidance and detachment from most people, social isolation, and periods of numbing and dissociation during which she described herself as feeling very vulnerable and stressed to the point of not even being able to feel her feelings. Her comorbid diagnoses were bipolar disorder not otherwise specified (DSM-IV), opioid dependence in full remission for 15 years, and hypertension. Her DHEA sulfate level of 34 μg/dL was near the bottom of the normal range (32–240 μg/dL).

Within a few days after starting treatment with 7-keto DHEA 25 mg daily, Ms. B reported feeling much better. She was calmer, she experienced much less anger and irritability, and her mood became more stable. She said she is now finding it easier to do well in school because she is better able to focus when studying and attending class, adding, "Now I'm better able to remember what I've read." Ms. B also reported having an easier time socializing and a renewed interest in sex after having had no sexual interest at all for a month. Within 2 weeks after starting on 7-keto DHEA, she felt calm and centered enough to return to work, attended a job interview in which she performed very well, and was quickly offered a job at a local hospital.

Case 3. Ms. F, a 52-year-old woman with chronic severe PTSD associated with a history of severe physical and sexual abuse beginning in childhood (age 5), had remained highly symptomatic despite attending group and individual CBT sessions for 17 months and receiving treatment with sertraline 250 mg and topiramate 225 mg daily and quetiapine 75–100 mg at bedtime. She was also on a methadone maintenance dose of 60 mg daily. Her symptoms included irritability, mood lability, crying, difficulty sleeping, nightmares from which she would wake up screaming, flashbacks, hypervigilance, and frequently feeling fatigued, depressed, and lonely. Her affect was constricted and distant, she was quick to feel offended or alienated, and she reported feeling detached from others.

Ms. F's comorbid diagnoses were major depressive disorder, recurrent, moderate; rheumatoid arthritis; hepatitis B; gastritis; asthma; and obesity. Her DHEA sodium level was low (19.8; normal range, 42–290 μg/dL).

After 4 days on treatment with 7-keto DHEA 25 mg daily in 2005, Ms. F said she felt better and was no longer getting anxious and overwhelmed by stressful events. She also reported having better memory; i.e., she found appointments easier to remember.

Ms. F appeared better socially related, was less guarded and pessimistic, had less constricted affect, maintained better eye contact, and was more productive and open in her communication. Seven days after starting on 7-keto DHEA treatment, she reported having fewer nightmares and flashbacks and that, when they occurred, they were less frightening and upsetting. She also said she felt more relaxed and was no longer crying or getting very upset when she experienced anger.

Case 4. Ms. D, a 59-year-old woman, was in psychiatric treatment for over 25 years, including a long course of psychoanalysis and 2 years of CBT. She had been treated with adequate trials of 2 tricyclic antidepressants, 3 SSRIs, venlafaxine, 2 monoamine oxidase inhibitors, 3 anticonvulsants, many typical and atypical antipsychotics, lithium, bupropion, trazodone, and nefazodone. The only medications that gave her some relief from anxiety, depression, and agitation were occasional lorazepam 1 mg p.r.n. and aripiprazole 2.5 mg daily. Pemoline 75 mg daily and phentermine 30 mg daily gave her enough energy to function. Methylphenidate, dextroamphetamine, and other stimulants had been tried but all made her anxiety worse.

In spite of all of the treatment she had received, Ms. D continued to experience severe symptoms of anxiety, fearfulness, irritability, and difficulty concentrating. These symptoms interfered with her ability to socialize with friends and family, learn new information, and integrate and retain the skills she was being taught in CBT. She was referred 14 years ago for treatment-resistant depression but, as more clinical information became available, was rediagnosed by her treating psychiatrist and psychologist as having PTSD with dissociative identity disorder (both DSM-IV). She suffered from physical, emotional, and sexual abuse as a child but would never discuss details because it was too disturbing to her.

She was treated with 7-keto DHEA 50 mg for 6 weeks in 2005, which led to some improvement in daily functioning and more positive affect. The dose was increased to 100 mg for 6 weeks to achieve more significant improvements. She became much more social and said she was able to read and enjoy complex intellectual material for the first time since childhood. Ms. D also gained the ability to use skills for emotion regulation from the dialectic behavior therapy that she had been receiving (with a Ph.D.-level psychologist experienced in treatment of PTSD) for the previous 2 years. Her dose was increased to 150 mg daily at the time of this report, and she feels she is continuing to improve.

Case 5. Ms. E, a 55-year-old woman referred by her psychiatrist, had a lifelong history of anxiety, PTSD, dissociative identity disorder, panic attacks for more than 30 years, agoraphobia, frequent visits to emergency rooms with conversion symptoms such as uncontrollable pelvic thrusting movements, social anxiety disorder, irritability, depression, and lack of energy and libido. She was raised in a rigid, excessively strict Protestant family and had a history of childhood physical and verbal abuse. She refused to discuss possible sexual abuse.

Her symptoms persisted in spite of psychotherapy for more than 15 years and numerous trials on medications. She was treated with sertraline for 6 years (1994–2000) with minimal benefit. Venlafaxine was slightly helpful, but, while receiving a dose of 300 mg daily, she became overly activated and venlafaxine treatment had to be stopped. Ziprasidone and prochlorperazine caused severe dystonic-like reactions. Topiramate caused severe cognitive dysfunction. Quetiapine caused severe sedation, and aripiprazole caused a 30-lb weight gain.

Fearful of conventional psychotropic medication, and having developed type 2 (adult-onset) diabetes mellitus, Ms. E requested alternative approaches. she was begun on treatment with 7-keto DHEA 25 mg daily in 2005, raised after 1 week to

50 mg and after 4 weeks to 75 mg daily to achieve fuller remission. She reported feeling calmer and being better able to deal with the stress of her mother's death and with settling the estate, as well as experiencing less need to overeat to soothe herself. She said she had more focus, had more creative ability in her writing, and no longer needed to talk to herself when alone. She also began to exercise and lose weight. Ms. E said that she felt this was the first medication ever to help her.

In addition to the severe problems with dissociation present in patients 1, 4, and 5 and the numbing and avoidance seen in patients 1 and 2, all 5 patients presented with irritability, decreased energy, decreased memory and concentration, depressed or labile mood, decreased libido, anxiety, insomnia, and crying, reminiscent of the psychiatric symptoms seen in Cushing's disease.[4–6] A number of studies and case series have demonstrated an improvement in these types of symptoms following cortisol-lowering treatments in patients with major depression and in patients with Cushing's disease.[5,7–10]

One open series[11] and 3 placebo-controlled, double-blind, randomized trials[10,12,13] have supported the effectiveness of DHEA in midlife major and minor depression or dysthymia. Several recent reviews have also discussed data on DHEA to enhance memory, cognition, sexual functioning, and well-being in healthy elderly individuals and in patients with adrenal insufficiency.[14,15]

As reported by Schmidt et al.[10] and others,[16,17] DHEA stimulates neurogenesis and synapse spine formation in the rat hippocampus and prevents corticosterone-induced neuronal damage. Similarly, studies have shown 7-keto DHEA to be a "natural antiglucocorticoid," able to counteract the effect of circulating glucocorticoids such as cortisol, in mice whose immune functioning was compromised (either by chronic stress or by an immune-suppressing drug)[18,19] and able to interfere with the normal uptake of activated glucocorticoid receptors,[20] with evidence showing that it may confer neuroprotection.[21,22]

The study by Rasmusson et al.[23] of 13 women with chronic PTSD showed that a higher level of DHEA in response to adrenal activation by adrenocorticotropic hormone was associated with less severe PTSD symptomatology and that a higher ratio of peak DHEA to cortisol was associated with less-severe negative mood symptoms. Morgan and colleagues' study of 25 elite special operations solders during prolonged and extreme training stress showed that subjects who reported fewer symptoms of dissociation and exhibited superior military performance had significantly higher ratios of DHEA sulfate to cortisol.[24]

DHEA and its 7-oxo derivative were both tested for their effect on water maze memory in young and old mice. While both were effective in young mice in reversing the memory impairment caused by scopolamine, only the 7-oxo derivative succeeded in improving memory retention in the old mice studied.[25]

While there have been a number of articles written about DHEA, some of which are discussed above, this, to the best of our knowledge, is the first report of the benefits of 7-keto DHEA in treating symptoms associated with severe early trauma, including dissociation, avoidance and numbing, reexperiencing, hyperarousal, anger, and affective instability. The outcome of this small case series offers intriguing preliminary evidence that 7-keto DHEA may be beneficial in treating patients with histories of severe early trauma and persistent refractory PTSD. Further controlled studies are needed to confirm this impression. In the first 4 cases, 7-keto DHEA was added as an adjunct to the patients' other medications; in case 5, it was used as a single agent. Future research should include controlled trials of 7-keto DHEA both as an adjunct and as a single agent in treating patients with histories of severe trauma as well as persistent refractory trauma and affective symptoms.

The formulation of 7-keto DHEA is made by Smart Nutrition (San Diego, Calif.) in the form of capsules containing 25 mg of the active compound. It was obtained over the counter by patients either at their local pharmacies or by calling a toll free number (800-479-2107). It is inexpensive. Patient 3 purchased her bottle of 60 pills for under $13 at a local pharmacy; thus, the cost of treatment was $1.59 per week.

It is important to note that 7-keto DHEA has a major advantage over DHEA in that it is not aromatized to testosterone or estrogen, which can result in risks seen with increased testosterone (such as acne, baldness, hirsutism, voice changes, prostatic effects) or elevated estrogens (such as increased risk of uterine or breast cancer, vaginal bleeding or endometrial hyperplasia, or venous thromboembolism). There are no known important drug interactions, and in a study by Davidson et al.,[26] it caused no side effects or changes in clinical laboratory values. Although there are no case reports of induced mania with 7-keto DHEA, induced mania has been reported with DHEA and it may be a possibility with 7-keto DHEA.[27,28] None of the 5 patients on 7-keto DHEA treatment reported any negative side effects, and all have continued to show further gains in mental functioning.

Dr. Sageman has served on the speakers bureaus of Pfizer, GlaxoSmithKline, and Bristol-Myers Squibb. Dr. Brown has served on the speakers bureau of Pfizer.

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Sharon Sageman, M.D.
Department of Psychiatry
St. Luke's-Roosevelt Hospital
New York, New York
Richard P. Brown, M.D.
Department of Psychiatry
Columbia University, College of Physicians and Surgeons
New York, New York

Exacerbation of PTSD Symptoms With Use of Duloxetine

Sir: Posttraumatic stress disorder (PTSD) is a common psychiatric disorder, with an estimated lifetime prevalence of 7.8%.[1] The prevalence of PTSD in Vietnam combat veterans is even higher at a rate of 30%.[2] Despite the common occurrence of this disorder, pharmacologic treatment studies are limited. In this case report, we present a Vietnam-era combat veteran with chronic PTSD whose symptoms were exacerbated by the use of duloxetine.

Case report. Mr. A, a 53-year-old married Vietnam veteran with DSM-IV-TR PTSD and bipolar disorder not otherwise specified, has been treated at the local Veterans Administration hospital since 1997. His PTSD symptoms include intrusive thoughts of Vietnam (occurring several times per week), occasional nightmares, avoidance of crowds, and mild hypervigilance. Despite their chronicity, these symptoms have been relatively well controlled with a combination of valproic acid, propranolol, and risperidone.

For the last several years, Mr. A has unfortunately also suffered from moderate depression with anhedonia, anergia, amotivation, concentration difficulties, lack of libido, and intermittent passive suicidal ideation. His depression has been refractory to numerous, adequate medication trials including nefazodone, fluoxetine, sertraline, citalopram, bupropion, venlafaxine, mirtazapine, trazodone, carbamazepine, lithium, and olanzapine. While some psychotropics helped initially then lost effectiveness, most provided no mood benefit. Trials of lithium and carbamazepine were aborted prematurely as they were not well tolerated.

In 2004, Mr. A was given a trial of duloxetine (60 mg/day); however, within the first week he experienced a severe exacerbation of PTSD symptoms including daily flashbacks of Vietnam, nightmares, emotional numbing, increased startle response, and extreme hypervigilance. He also had daily suicidal thoughts, which he attributed to his distress from the reexperiencing symptoms. His depressive symptoms otherwise remained unchanged. After his daily duloxetine dose was reduced to 30 mg, his PTSD symptoms lessened but remained higher than before treatment. Duloxetine was then discontinued altogether, and his PTSD symptoms returned to baseline.

Studies suggest that an overly sensitive noradrenergic system may underlie at least some of the symptoms of PTSD, including heightened startle response, hypervigilance, and increased arousal. Specifically, increased 24-hour urinary catecholamine,[3] 24-hour plasma norepinephrine,[4] and norepinephrine levels in the cerebrospinal fluid[5] have been noted in PTSD patients. Moreover, Morgan et al.[6] demonstrated that yohimbine, a noradrenergic agonist, increased the amplitude, magnitude, and probability of the startle reflex in combat veterans with PTSD as compared with combat controls. Noradrenergic antagonists such as propranolol, a β-blocker, and prazosin, an α_1-antagonist, have also been efficacious in decreasing arousal, reexperiencing, and numbing in PTSD.[7,8]

Duloxetine is a dual monoamine reuptake inhibitor affecting both serotonin and norepinephrine. Unlike its counterpart, venlafaxine, which affects norepinephrine concentrations only at doses at or above 150 mg,[9] duloxetine binds both serotonin and norepinephrine receptors with equal affinity even at low doses.[10] It seems likely that the noradrenergic effects of this medication were responsible for this patient's PTSD exacerbation. Further studies of duloxetine in the treatment of PTSD will better elucidate the significance of this finding. In the meantime, caution should be taken when prescribing this and other medications for PTSD that have potential noradrenergic effects.

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Michele L. Deneys, M.D.
Department of Psychiatry
University of Wisconsin
Eileen P. Ahearn, M.D., Ph.D.
William S. Middleton Veterans Hospital
Madison, Wisconsin

Methodological Issues in a Study of Long-Term Maintenance Therapy With Quetiapine Versus Haloperidol Decanoate

Sir: We would like to comment on the recently published study comparing long-term maintenance therapy of quetiapine with haloperidol decanoate in patients with schizophrenia and schizoaffective disorders.[1] On the basis of that study's poor methodological design and inadequate statistical computations, we wonder how the authors could arrive at any valid conclusion. Comparing an oral atypical antipsychotic (quetiapine) with an intramuscular conventional antipsychotic in an open-labeled design could skew the favorability bias toward quetiapine, especially in terms of reported side effects and efficacy. Moreover, the authors did not discuss the confounding effect that could result from doses that are not equivalent.[2] For example, the mean (SD) doses quoted in the study at 48 weeks were 493 (192) mg/day of quetiapine and 170 (45) mg/28 days of haloperidol decanoate. However, in terms of equivalence, 170 (45) mg/28 days of haloperidol decanoate is equivalent to 425 (112) mg/day of quetiapine.[2] Because a much higher dose of quetiapine was utilized, the efficacy could have been exaggerated.

It is well known that the higher the dropout rate in a study, the more difficult it is to draw any meaningful conclusion when comparing different active compounds.[3] Consequently, a small sample size of 29 and a dropout rate of almost 60% would have so incapacitated the generalizability as to render any conclusion meaningless. Another omission is the absence of a placebo arm. As a frame of reference,[4] a placebo arm would have provided comparatively interpretable values for the treatment effect, the reported side effects, and the dropout rates.

In the analysis section, there were 2 major flaws. Firstly, the authors reported a significant improvement in negative symptoms for quetiapine, at $p < .05$. In the absence of precision measurement such as confidence interval, this figure could be very misleading. We would have calculated the confidence interval if there had been enough data within the publication. Secondly, the authors did not account for the approximately 60% of patients who dropped out, thus neglecting the possibility of overestimating the comparative efficacy of quetiapine. A way of minimizing such bias would have been to use an intention-to-treat analysis in the form of last observation carried forward or worst case scenario.

In conclusion, the smallness of the sample size means that the study could not have been adequately powered to detect a difference in efficacy between the 2 interventions. Because of the study's open-label design, the potential for observation bias is huge and, coupled with a significant dropout rate, prevents the drawing of any meaningful conclusion.

Dr. Williams is a consultant to Abbott and is involved in a drug trial for Johnson & Johnson. Dr. Osinowo is on the speakers bureau of Pfizer. Drs. Adetunji, Basil, and Mathews report no financial or other relationship relevant to the subject of this letter.

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Babatunde Adetunji, M.D.
Department of Psychiatry
MHM-Correctional Services
Philadelphia, Pennsylvania
Biju Basil, M.D.
Maju Mathews, M.D., M.R.C.Psych.
Department of Psychiatry
Drexel University College of Medicine
Philadelphia, Pennsylvania
Adedapo Williams, M.D.
Department of Psychiatry
John Stroger Hospital of Cook County
Chicago, Illinois
Thomas Osinowo, M.D., M.S.
Department of Psychiatry
Northcoast Behavioral Health Care
Toledo, Ohio

Drs. Glick and Marder Reply

Sir: The authors of the letter raise a number of interesting issues.

They expressed a concern that the study[1] was biased toward quetiapine because of the open-label design and the use of a dose of quetiapine that was higher than the equivalent dose of haloperidol decanoate. We used an open-label design with blinded ratings in order to increase the external validity of the study. A double-blind design would have required that both groups of patients receive injections and pills. We continue to believe that this would have severely limited the generalizabil-

ity of the study findings, since patients who dislike injections would have been excluded from the trial.

The dosing of each drug was titrated by the study clinicians based on its tolerance and efficacy. It is likely that clinicians were able to achieve higher doses of quetiapine because of the drug's side effect profile. In effect, we intended to maximize external validity by determining the doses that patients could tolerate. And of course, as the authors are surely aware, we believed that the more important potential bias was that the patients receiving the decanoate would have better compliance (and therefore better outcome).

We acknowledge the limitations of the study due to the high dropout rate and small sample size. We used maximum likelihood estimation, which means that we included information from all subjects. This is a much better way of addressing the problem of dropouts than last observation carried forward or worst outcome carried forward. A placebo-controlled trial would have been interesting, but we are concerned that long-term studies with placebo do not provide adequate protection to patients with schizophrenia, who have a demonstrated need for antipsychotic maintenance.

In summary, we believe that the study suggests that many patients with schizophrenia can be successfully managed with oral second-generation agents rather than first-generation agents that require injection.

Dr. Glick has received grant/research support and honoraria from and has served on the speakers or advisory boards for AstraZeneca, Pfizer, Eli Lilly, Shire, Janssen, GlaxoSmithKline, and Solvay and is a major stock shareholder in Johnson & Johnson. Dr. Marder has received grant/research support from AstraZeneca; has received honoraria from Bristol-Myers Squibb; and has served on the speakers or advisory boards for Bristol-Myers Squibb, Pfizer, and Solvay.

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Ira D. Glick, M.D.
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine
Stanford, California
Stephen R. Marder, M.D.
Department of Psychiatry and Biobehavioral Sciences
David Geffen School of Medicine
University of California, Los Angeles
Los Angeles, California