Suicidal Ideation Associated With Duloxetine Use

A Case Series

To the Editors:

On May 2, 2007, the US Food and Drug Administration expanded black box warnings of all antidepressant medications to include information about an increased risk of suicidality in young adults aged 18 to 24 years. The advisory committee made this decision after evaluating the results of meta-analyses of participants enrolled in 372 randomized antidepressant trials over the past 20 years.

A differential risk of antidepressant-induced suicidality among various age groups has previously been reported in the literature. Martinez et al[1] found an increased risk of suicidality with selective serotonin reuptake inhibitors (SSRIs) compared with tricyclic antidepressants in patients 18 years and younger. Another case-control study found that severely depressed patients aged 6 to 18 years treated with antidepressants were at a significantly higher risk of suicide attempts and completed suicides compared with adults.[2] Elderly patients have been found to have nearly 5-fold higher risk of completed suicide during the first month of therapy with SSRIs.[3] The study also reported consistent results when venlafaxine was included in the analyses with SSRIs. Venlafaxine (which inhibits reuptake of 5-hydroxytryptamine [5-HT] and norepinephrine [NE] at higher doses) shares a similar proposed mechanism of action as duloxetine.[4] Duloxetine has been shown to have 100-fold higher affinity for human 5-HT transporters and at least 300-fold higher affinity for NE transporters in vitro compared with venlafaxine.[5] It is unknown whether more potent 5-HT and NE blockade correlates with increased suicidal ideation during initial antidepressant treatment.

CASE 1

Mr A is a 37-year-old married white man admitted for a major depressive episode after his wife discovered that he bought equipment to poison himself with carbon monoxide. Two months before admission, the patient started treatment with duloxetine for chronic back pain. The dose was later increased to 60 mg/d for additional pain relief. Two weeks before admission, duloxetine was increased again to 90 mg/d. Seven days later, the patient reported having thoughts of suicide and was admitted to the University of Kansas Medical Center psychiatry unit in August 2005.

Mr A had no previous psychiatric hospitalization or any outpatient psychiatric care. Before taking duloxetine, Mr A had never taken any psychotropic medications. He did not have prior suicidal attempts or suicidal ideations. No signs of character pathology or poor impulse control were elicited. The patient did have 3 first-degree relatives with an affective disorder but no family history of suicide.

Upon admission to inpatient psychiatry, Mr A appeared severely distressed. He continuously repeated the phrase: "My wife deserves better." Apparently, the patient developed a romantic interest with a woman at work. He denied any infidelity but started having guilt about the thoughts. Mr A's target symptoms also included anxiety, insomnia, and irritability. The patient was unable to state exactly why he wanted to commit suicide. Mr A reported that he did not feel sad and could think of no reason for him to wish to die. He described a loving and supportive marriage. Mr A was steadily employed with no recent additional social stressors.

On Day 1 of hospitalization, duloxetine was tapered off, and escitalopram was started. The patient was also started on risperidone 1 mg at bedtime for psychic agitation. Within days of discontinuing duloxetine, Mr A reported decreased anxiety and no thoughts of suicide. After 3 days, he was discharged home on escitalopram and risperidone.

CASE 2

Mr B is a 63-year-old well-educated married white man admitted to the University of Kansas Medical Center psychiatry unit in August 2005. The patient presented with a chief complaint of "I started having thoughts of suicide." Mr B had a previous history of major depressive disorder (MDD) successfully treated with fluoxetine. Four months before admission, the patient did not feel depressed and stopped taking fluoxetine. Depression reoccurred; 2 weeks before admission, the patient was started on duloxetine at an initial dose of 30 mg/d for mild symptoms of depression (eg, fatigue, insomnia, and sadness). The patient felt no significant improvement, and duloxetine dose was increased to 60 mg/d. During this period, the patient was not taking any other medications. The patient soon started having obsessive thoughts about suicide together with severe anxiety, insomnia, and irritability. He was unable to explain why he was having thoughts of wanting to die. Mr B then sought the help of an outpatient psychiatrist, and duloxetine was tapered off, and fluoxetine was restarted. Two days later, the patient expressed concern about having the thoughts of suicide, and his psychiatrist recommended inpatient hospitalization.

Upon admission, fluoxetine was increased to 60 mg/d, and mirtazapine was added at bedtime for depression and insomnia. Five days after stopping duloxetine, the patient reported decreased anxiety and no longer had thoughts of death or suicide.

Mr B did not have a history of a suicide attempt or any thoughts of suicide before treatment with duloxetine. No symptoms suggestive of character pathology or poor impulse control were noted. The patient did have a first-degree relative with a history of suicide. Mr B described having a loving and stable family. The patient did experience a recent increase in workload after a coworker was let go. He did not attribute the depressive symptoms to work-related stress.

CASE 3

Ms C is a 39-year-old married white woman with a 20-year history of MDD and chronic fatigue syndrome. She was admitted to inpatient psychiatry after she and her husband became concerned about her worsening depressive symptoms. This was her first psychiatric hospitalization because her depressive symptoms had been well controlled with antidepressant monotherapy, including fluoxetine and escitalopram (discontinued by the patient 10 months before admission). She had attempted suicide by carbon monoxide poisoning 10 years before this admission, escaping from her garage after developing a headache.

Three months before admission, Ms C had been started on duloxetine 30 mg/d. Duloxetine was titrated to 90 mg/d over the

next 4 weeks. She reported experiencing almost no change in her depressive symptoms but had noticed an improvement in weakness and pain associated with chronic fatigue syndrome. Duloxetine was increased again to 120 mg/d. At a follow-up visit 6 weeks later, her depressive symptoms had worsened; she felt more hopeless, worried, and isolated, with increased anxiety and poor sleep. Six days later, in February 2006, she was admitted to the University of Kansas Medical Center psychiatry unit.

At the time of admission, she reported having thoughts of suicide and of her children drowning in their swimming pool. She emphatically denied any intentions of killing her children but was filled with fear that if they should drown, she would have lost her remaining reason for wanting to live. She reported feeling "drugged" and losing control of her thoughts. Her husband reported that these thoughts were uncharacteristic of his wife and a source of great concern. During treatment with duloxetine, Ms C also developed a significant problem with urinary retention. Duloxetine was tapered over several weeks, resulting in an abatement of the thoughts of suicide and her children drowning and a resolution of urinary retention.

CASE 4

Ms D is a 42-year-old white woman, who was admitted to the Kansas City VA Medical Center after she presented herself to the mental hygiene clinic complaining of increasing suicidal ideation for the previous 5 days. Two weeks before admission, the patient had been switched from fluoxetine 40 mg/d to duloxetine 40 mg/d because of persistent diarrhea. The patient reported thoughts of poisoning herself in an enclosed garage with carbon monoxide and thoughts of overdosing with clonazepam. She reported vivid flashbacks of experiences with her former husband 20 years before when he had threatened to kill himself by holding a gun to his head. Ms D's target symptoms also included decreased concentration, decreased sleep, poor appetite, decreased energy, anhedonia, and increased agitation.

Upon admission to inpatient psychiatry, Ms D was quite tearful and reported that this was the first time that she had ever had thoughts of suicide. Ms D had no previous psychiatric hospitalization. Ms D had been diagnosed with MDD and posttraumatic stress disorder in 1995. Previous treatment had included citalopram, fluoxetine, bupropion, gabapentin, and clonazepam. Current medications included duloxetine 40 mg/d, clonazepam, and naproxen. Upon admission, duloxetine was discontinued, and fluoxetine 20 mg/d was restarted. Three days after stopping duloxetine, the patient reported

having no thoughts of suicide, no insomnia, and improved appetite. She was noted to be interacting well with peers and staff. She reported that her mood was positive, and she felt "100%" better after restarting fluoxetine. Subsequently, Ms D was discharged home on her third hospital day.

DISCUSSION

The authors present 4 cases that illustrate a close temporal relationship between the development of acute suicidal ideation and duloxetine use. In all 4 cases, suicidal thoughts appeared after increasing duloxetine dosages and subsided after discontinuing use. The patients were medically stable, with laboratory results within normal limits. None had recent substance abuse or dependence. No extrapyramidal symptoms were noted.

Duloxetine is currently approved by the Food and Drug Administration for treatment of MDD, generalized anxiety disorder, and diabetic peripheral neuropathic pain. Multiple clinical trials have demonstrated efficacy of duloxetine for treatment of stress urinary incontinence and fibromyalgia.[6–9] A review of controlled studies of duloxetine for MDD found no difference between duloxetine and placebo in respect to measures of suicidal ideation and behaviors.[10] However, it is unclear what exclusion criteria in regard to suicidal ideation or behaviors were applied to patients entering these studies. It is also unknown whether the results would have been different if non-MDD duloxetine clinical trials were included in the analysis.

To our knowledge, this is the first case series to describe development of suicidal preoccupation in conjunction with duloxetine use. Clinicians should carefully monitor patients for emergence of suicidal ideation when prescribing any antidepressant, with particular scrutiny during periods of initial use and dosage increases.

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Successful Treatment of Nicotine Withdrawal With Duloxetine
A Case Report

To the Editors:

Mrs D is a 38-year-old woman, mother of a 5-year-old boy, without psychiatric history. She had developed a major depressive disorder and alcohol dependence (6 to 8 beers per day) after her divorce 2 years earlier. She had since then lost her job as a secretary because of her difficulties to concentrate

and was socially isolated. During the past 2 years, she had been admitted twice in the psychiatric emergency service for alcohol abuse and suicidal thoughts but had never followed an adequate treatment. She was treated for a few weeks by mirtazapine, 30 mg/d, with a slight improvement of her depressive state, but stopped it because of weight gain. She had also tried paroxetine, 20 mg/d, but was not compliant with it and stopped it eventually. Her depressive symptoms consisted of depressed mood, irritability, insomnia, loss of appetite, guilt, markedly diminished interest and pleasure in almost all activities, difficulties to concentrate, and suicidal thoughts. The results of the somatic evaluation, electrocardiogram, routine blood screening, and neurological examination including a cerebral computed tomographic scan were all normal.

Mrs D had been experiencing nicotine dependence since many years and smoked 30 to 40 cigarettes per day—the first one within 10 minutes of awakening. She had already tried to stop smoking and had presented symptoms of nicotine withdrawal including depressed mood, anxiety, irritability and anger, insomnia (waking in the middle of the night), increased appetite with weight gain, and craving for cigarettes. Her score on the Fagerstrom Test for nicotine dependence was of 8 and therefore consistent with a physical syndrome of nicotine dependence.

In January 2007, an ambulatory psychiatric follow-up consisting of supportive therapy was started, and a treatment of duloxetine 60 mg/d was introduced, followed by marked improvement of her depressive symptoms and reduction of her alcohol consumption to 1 or 2 beers per day. She stopped smoking, without using any nicotine substitution product such as nicotine patches. She did not complain of any nicotine withdrawal symptoms such as anxiety or insomnia and did not crave for cigarettes. She observed a weight gain of 4 kg and adverse skin reactions that were diagnosed as acne. These were associated to a possible side effect of smoking cessation.[1] However, she felt relieved to have stopped smoking. Two months later, she found a new job, started a new relationship, and had not smoked again. In June 2007, we had the opportunity to verify the self-reported smoking cessation by salivary cotinine measurement using the method described by Etter et al.[2] Indeed, Mrs D had cotinine levels below 10 ng/mL that is the conventional threshold used to distinguish smokers from nonsmokers.[3]

DISCUSSION

We have here described the case of a woman who stopped smoking and reduced her alcohol intake on a regimen of 60 mg/d of duloxetine. This observation is supported by another case report describing a man who stopped, 1 week after the introduction of duloxetine at 60 mg/d, a cigarette habit in which he had been consuming one-half pack per day for at least 20 years.[4]

Nicotine is one of the most widely used drugs, with increasing frequency among adolescent and young adults. Cigarette smoking is associated with cardiovascular and pulmonary diseases and is one of the leading causes of death in the world. Many cigarette smokers are not able to quit even after numerous attempts and the use of specific medications. Low educational level, substance abuse, and psychiatric comorbidities have all been associated with difficulty to quit.[5] Moreover, women seem to be less sensitive to nicotine replacement therapies and to display more symptoms of depression during withdrawal than men.[6] The development of novel and more effective pharmacological approaches for smoking cessation and management of withdrawal symptoms is therefore crucial.

Two thirds of regular smokers experience withdrawal symptoms including craving, restlessness, increased appetite and weight gain, irritability, and anger.[7] In addition to standard treatment regimen (nicotine patches therapy or gums), the pharmacological treatment of nicotine dependence with antidepressants has received considerable attention from the clinical community. Antidepressant medications have an action on central neurotransmitter systems, including serotonin (5-hydroxytryptamine [5-HT]), dopamine (DA), and noradrenaline (NA) that are involved in affect regulation, a critical factor in treatment success.[8] Among antidepressants, bupropion and nortriptyline have been proposed for treatment of nicotine dependence.[9] Bupropion inhibits neuronal NA and DA reuptake and is thought to reduce tobacco withdrawal symptoms by enhancing central DA concentrations. Clinical studies showed that bupropion is effective in both initial smoking cessation and relapse prevention. Its antidepressant and antismoking effects seem to be independent. However, bupropion has not been effective in every case, and there is controversy about the subtypes of smokers for whom it might be used.[9] Nortriptyline is a tricyclic antidepressant that increases the synaptic concentration of NA and 5-HT by blocking their reuptake. Nortriptyline has little or no effect on the dopaminergic system but demonstrates a potent norepinephrine (NE) activity and has also been shown to aid smoking cessation.[9] Selective serotonin reuptake inhibitors, which are selective for 5-HT, are not useful forsmoking cessation. Antidepressants with NA and/or DA activities should therefore be considered as molecules of choice.

Recent studies focused on treatment of smoking dependence by dual reuptake inhibitors, also called serotonin noradrenalin reuptake inhibitors, such as venlafaxine and duloxetine. Venlafaxine and duloxetine inhibit, in a dose-dependent manner, the reuptake of both 5-HT and NA and also, at a lower level, of DA. This mechanism of action contrasts with the effect of reuptake inhibition by tricyclics, which results in elevation of 5-HT and NA but not of DA. Serotonin noradrenalin reuptake inhibitors typically block 5-HT at a lower dose; 5-HT and NE at medium to high dose; and 5HT, NE, and DA at the highest dose.[10] However, secondary amines such as nortriptyline tend to enhance NE and 5-HT at 3:2 ratios, and this ratio does not depend on the blood level of the drug. The capacity to enhance DA concentration is probably one of the core mechanisms of serotonin noradrenalin reuptake inhibitors in the treatment of dependence. Indeed, venlafaxine has been used in the treatment of cocaine dependence and was shown to be effective in the treatment of lighter smokers.[8] Compared with venlafaxine, duloxetine displayed higher affinity for both the 5-HT and NA reuptake transporters.[10] In addition, duloxetine is more potent than venlafaxine in inhibiting DA transporter.

These discrepancies could explain why duloxetine is more effective than venlafaxine in the treatment of nicotine and other substance dependence by causing a greater increase of DA in strategic brain structures.[10]

Several neurotransmitter systems have been implicated in the process of smoking maintenance and relapse, including 3,4-dihydroxyphenylalanine, NA, 5-HT, acetylcholine, endogenous opioids, γ-aminobutyric acid, glutamate, and endocannabinoids. However, most of the symptoms associated with smoking cessation are thought to be mediated by DA.[11] Nicotine, the main psychoactive component in cigarettes, has a central effect by acting on neuronal nicotinic-acetylcholine receptors that are found in the cell bodies and terminals of DA-containing neurons. The mesolimbic dopaminergic system is a key component of the reward pathways formed by projections form the ventral tegmental area in the midbrain to anterior limbic forebrain structures such as the nucleus accumbens and the cingulated cortex.[12–14] It is now widely accepted that increased levels of DA, especially in the nucleus accumbens, are involved in the rewarding effect. Moreover, it is likely that hypoactivity of the dopaminergic projections plays a role in craving and drug seeking during the early stages of abstinence. Therefore, drugs such as duloxetine that increase dopaminergic transmission in these brain areas and particularly in the nucleus accumbens should be effective in the treatment of nicotine addiction.

Many refractory smokers have comorbid psychiatric and drug abuse disorders and are therefore less sensitive to standard treatments for nicotine dependence. Symptoms such as depressed mood, anxiety, irritability, concentration difficulties, bradychardia, somatic complaints, and increased appetite are typically associated with abrupt cessation of tobacco smoking.[15] In our patient, duloxetine was effective in reducing depressive and nicotine withdrawal symptoms. Our case report suggests an independent effect of duloxetine on the reward pathways, probably mediated by its dopaminergic action on the nucleus accumbens. This independent effect seems to be supported by the reduced need for alcohol shortly after the introduction of duloxetine in our patient. The action of duloxetine on DA seems to be the key component of its effectiveness on smoking cessation and could suggest an effect not only on nicotine withdrawal symptoms but also on other drug withdrawal symptoms such as those of alcohol and cocaine. In this perspective, venlafaxine has already been shown to be useful for cocaine dependence. The unique profile of duloxetine on 5-HT, NA, and DA systems warrants further studies to establish its role in the treatment of drug dependence.

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Duloxetine-Induced Cutaneous Adverse Reaction

To the Editors:

Cutaneous adverse reactions to antidepressants have been reported with several chemical classes thereof, including tricyclics, selective serotonin reuptake inhibitors, bupropion, and selective serotonin and norepinephrine reuptake inhibitors (SNRIs), although not as yet with the newer SNRI duloxetine (DUL).[1–3] In the following, we report on such a case, whereby the patient's cutaneous reaction can be attributed to DUL.

A 48-year-old premenopausal female subject with a major depressive episode of moderate severity but chronic course was referred for treatment to our department. The patient had been resistant to a multitude of antidepressant agents received as an outpatient during the last year, including several tricyclics and selective serotonin reuptake inhibitors, as well as the SNRI venlafaxine and the noradrenergic and serotoninergic antidepressant mirtazapine. Owing to her lack of response to these agents, we opted for the newer SNRI DUL, dosed at 60 mg/d. Within 2 days after starting treatment, the patient developed a generalized mildly pruritic rash accompanied by edema in the periorbital area. Duloxetine was immediately discontinued, and with the aid of histamine-1-receptor antagonists, both her rash and edema subsided within the following 4 days. Thereupon, DUL was reinstated, however, at a precautionary lower dosage (30 mg/d). Nevertheless, only 2 hours after receiving the first dose, the patient's generalized rash relapsed, accompanied this time by hoarse voice, tongue swelling,

and dyspnea, prompting the psychiatrist on duty to administer on the spot hydrocortisone 500 mg IV Again, DUL was discontinued, and patient's symptoms resolved within the following 10 days, with the help of corticosteroids and histamine-1-receptor antagonists. Of note, the patient reported no past allergic reactions to any other medications of the same or different categories. The application of the Naranjo adverse drug events scale[4] to the data of our case yielded a score of 9 (maximal possible score on the adverse drug event scale, 13), which allows us to infer that the probability of DUL having caused the patient's clinical picture was quite strong.

In a recent analysis of pooled data relevant to DUL's safety and tolerability in the treatment of major depressive episode, rash as an adverse event leading to treatment's discontinuation was reported in 0.4% of patients under DUL and in 0.3% of patients under placebo.[5] However, since the between-group differences were minimal, any attribution of rash's emergence to DUL would be highly doubtful. Still, in another smaller study of relevant pooled data, rash not otherwise specified was reported in 0.8% of patients under DUL at 60 mg/d versus 0% in patients under placebo.[6]

In conclusion, given the total lack of published case reports and the insufficient clarity of controlled studies on these topics thus far, our report provides some clear, although admittedly circumstantial, evidence on DUL's potential to bring about relatively severe cutaneous reactions, a possibility that thus has to be taken into account by prescribers of psychotropic drugs.

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Successful Treatment of Chronic Fatigue Syndrome With Duloxetine and Trijodthyronine—A Case Study

To the Editors:

Chronic fatigue syndrome (cFS) is characterized by disabling fatigue associated with complaints of fevers, myalgia, lymphadenopathy, and depression. The pathophysiology of cFS is still poorly understood. Most patients suffering from cFS have elevated IgG serum antibodies to common viruses.[1] Several authors believe RA27/3 rubella immunization to induce cFS in predisposed individuals.[2] It is still unclear whether the modifications of the proportion of lymphocyte subsets found in patients afflicted with cFS are a cause or a consequence of this chronic illness.[3] An elevation of either the protein levels or the number of cells[4] can be detected in the cerebrospinal fluid (CSF) of approximately 30% of the cFS-patients from whose body liquids, *no* specific infectious causal agent could be isolated. Depressive symptoms associated with cFS are often treated successfully with selective serotonin reuptake inhibitors (eg, paroxetine). There is no effective treatment of painful physical symptoms of cFS known so far. In treatment of overall painful severity, the combined serotonin and norepinephrine reuptake inhibitor duloxetine is superior to the selective serotonin reuptake inhibitor paroxetine.[5] To our knowledge, there is no previous report of treatment of cFS with duloxetine.

In this study, we report the successful treatment of a patient suffering from cFS with duloxetine augmented with trijodthyronine. The application of this combination therapy resulted in an alleviation of both her psychic and her somatic symptoms.

Ms A, a 26-year-old woman, is reported to having developed first symptoms of cFS after a severe common cold 2 years ago. From then on, she has been continuously afflicted with different symptoms of cFS. Predominantly, she suffers from a series symptoms affecting her daily activity: Increased somnolence, feeling of "tiredness," unusually "low energy," and difficulties to concentrate. All over her body, myalgia is the most prominent symptom she is afflicted with. Clinical and neurological investigations, including cranial nuclear magnetic resonance and investigations of the cardiovascular system, revealed no pathological findings. We detected an elevated white cell account (normal: < 5 cells/μL) and signs of intrathecal antibodies (Table 1) in her spinal fluid. Due to those laboratory signs of central nervous inflammation, we were not able to rule out clinical encephalitis, and the patient was consequently treated with acyclovir (1.5 g/d, for 10 days), which did not lead to clinical improvement. More specific analysis of her CSF revealed an enhancement of the specific rubella-antibody index (Table 1).

Then we started a symptomatic therapy with amantadine (amantadine [50 mg/d])—as reported in by Gottschalk et al.[6] In approximately 2 weeks, tiredness and low energy were improved, whereas the dimension of myalgia did not change. Therefore, we decided to apply duloxetine (cymbalta in a dosage of 120 mg/d). Successful treatment with a similar drug, called venlafaxin, has been reported in a case study.[7] Duloxetine has been shown to be a powerful analgetic and antidepressive drug.[8–10]

TABLE 1. Laboratory Results

Cerebrospinal Fluid (CSF) Findings	Baseline	Week 2	Week 4	Week 12
Cell counts (≤4 cells/μL)	17	24	15	9
Lymphocytes, %	60	61	65	62
Lymphocytes (activated), %	23	28	16	20
Total protein, mg/L	398	307	345	337
Lactat, mmol/L	1.3	1.3	1.2	1.4
Albumin$_{(Q \ CSF/serum)}$ × 10^{-3} (<5.7 × 10^{-3})	5.97	5.00	5.84	6
IgG$_{(Q \ CSF/serum)}$ × 10^{-3}	4.2	3.7	3.8	4.5
Intrathecal synthesis, %	3.2	6.7	0	0
IgA$_{(Q \ CSF/serum)}$ × 10^{-3}	1.6	1.6	1.7	2.1
Intrathecal synthesis, %	0	0	0	0
IgM$_{(Q \ CSF/serum)}$ × 10^{-3}	2.3	2.4	2.2	2.5
Intrathecal synthesis, %	42.5	59.8	45.7	42.5
Oligoclonal bands	Pos	Pos	Pos	Pos
Antibody index borrelia	Neg			
Antibody index early summer meningoencephalitis	Neg			
Antibody index rubella	Pos (4.2)			Pos (4.1)
Antibody index varicella zoster virus	Neg			
Antibody index HSV1/2	Neg			
Antibody index measels	Neg			
Antibody index lues	Neg			
Antibody index HIV 1/2	Neg			
Antibody index HHV6	Neg			

Under the treatment with duloxetine, most symptoms of cFS disappeared within 4 weeks and no adverse drug effects occurred. Three months later, under continuous medication with duloxetine, Ms A developed a relapse with daily somnolence, a strong feeling of tiredness, and the feeling of low energy. Interestingly, myalgia did not reappear. In the spinal fluid, we still found inflammation signs in her CSF (but *not* in her *blood*) like an elevated white cell account and elevated amount of intrathecal antibodies (Table 1).

At this point, the most prominent symptom reported by the patient was her feeling of never being really awake, combined with stiffness of her muscles and difficulty in moving extremities. Because we believed these symptoms to be caused by low intracellular T3 levels or disturbances of the T3-thyroid hormone functions,[11] we added trijodthyronine (thybon [20 μg/d]) to the continues medication with duloxetine. Within 2 weeks, all symptoms disappeared almost completely. Twelve months later, she still continued to show improvement in her overall function. Serum natural killer (NK) cell activity in terms of cytotoxic function improved

with the combination therapy of duloxetine [120 mg/d] and trijodthyronine [20 μg/d] (see below). Cortisol and dehydroepiandrostenedione are at normal level. Previous studies showed controversial results of hormone levels of cortisol and dehydroepiandrostenedione in patients with cFS.[12]

The pathobiology of cFS is still poorly understood. One commonly held hypothesis is that cFS is caused by viral infection leading to chronic low-level activation of the immune system. This immunological activation is postulated to alter neurotransmitter functions and to lead to clinical symptoms seen in cFS. Immune regulation within the central nervous system seems to be involved in the pathobiology of cFS. Numerous immunological abnormalities have been inconsistently reported. However, the result of an initial examination of Ms A revealed an NK cell activity of 9% (normal range: >25%). A small stimulation of NK cell activity by interleukin 2 up to 23% (normal range: >40%) has been found. This NK cell subset is known in patients with cFS[3,7,13] and improvements in immunological abnormalities are shown to be correlated with remission of cFS.[7]

Improvements of the function of the NK cell subset have been seen in our patient under the continuous combination treatment with duloxetine and trijodthyronine: NK cell activity increased from 9% to 25% after 12 weeks and increased further up to 46% after 52 weeks (normal range: >25%). Similar to these findings, stimulation of NK cell activity by interleukin 2 raised from 23% to 26% after 12 weeks and further up to 57% after 52 weeks (normal range: >40%).

First improvements in clinical symptoms (under treatment with duloxetine) were a complete remission in body myalgia and a reduction in difficulties to concentrate in less than 4 weeks. Under the following combination of duloxetine (120 mg/d) and trijodthyronine (20 μg/d), the feeling of tiredness, unusually low energy, difficulties to concentrate, the feeling of never being really awake combined with stiffness of her muscles and difficulty in moving extremities disappeared within 2 weeks.

Many studies demonstrate the involvement of both the central and the autonomous nervous system, as well as the involvement of a selective immune dysfunction in the pathophysiology cFS. The analysis of the CSF of our patient showed impairment of her blood-brain barrier, an elevated white blood cell count in the CSF and prominent intrathecal IgM synthesis (Table 1). Approximately 30% of the cFS patients display an impairment of their blood-brain barrier and show elevations in white blood cell count compared with laboratory norms.[4] Nevertheless, this is the first report of a cFS patient displaying an elevated white blood cell count in spinal fluid combined with prominent IgM synthesis intrathecal. Chronic fatigue is also one of the major symptoms of Mollaret meningitis. This meningitis is (similar to cFS) characterized by disabling fatigue associated with complaints of fevers, myalgia, and strong neck pain for at least several days. In the CSF of patients with Mollaret meningitis, up to 10% large activated monocytes ("mollaret's cells") can be found.[14] In our patient, we did not find any of those pathognomonic "Mollaret's cells." Furthermore, we found decreased circulating natural killer cells in the serum. We did not find elevated levels of NK cells as described

for Mollaret meningitis.[15] Even though clinical aspects and the medical history of our patient were concordant with the symptoms of this rare meningitis, the above-mentioned laboratory findings argue against the diagnosis of Mollaret meningitis. Dechene[11] hypothesized that the cFS seems to be due to disturbances of insulin and trijodthyronine hormone. It has been shown in mice that trijodthyronine plays an important role in the modulation of NK cell activity. Those animal models provided new insights into the pathophysiology of the chronic fatigue syndrome and the interrelation of the endocrine and the immune system.[16] Based on our experience with the case of Ms A and the literature reviewed, we have come to the conclusion that duloxetine and trijodthyronine might be an effective combination treatment regime for cFS, leading not only to clinical improvement but also to a beneficial impact on a possible immunological basis of the disease.

For this study, written informed consent and human subjects research committee approval were obtained.

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Combining Mirtazapine and Duloxetine in Treatment-Resistant Depression Improves Outcomes and Sexual Function

To the Editors:

One frequently underestimated reason for antidepressant drug discontinuation is sexual dysfunction. Although 50% of untreated depressed patients report difficulties with sexual function,[1] antidepressant-induced sexual dysfunction has been reported in up to 70% of patients treated with selective serotonin reuptake inhibitor (SSRI) or serotonin/norepinephrine reuptake inhibitor antidepressants.[2]

Duloxetine, a balanced serotonin and norepinephrine reuptake inhibitor with comparable antidepressant efficacy to SSRIs and venlafaxine,[3,4] is associated with a moderate level of sexual dysfunction.[5] Mirtazapine, a noradrenergic and specific serotonergic antidepressant, is often used as an alternative treatment in patients having SSRI-induced sexual dysfunction.[6,7] To our knowledge, the effect of adding mirtazapine to duloxetine on sexual dysfunction has not been reported. This case series examined effectiveness and sexual side effects of adding mirtazapine in patients who failed to respond to duloxetine monotherapy.

Twelve subjects, meeting criteria for major depression (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*) with baseline Hamilton Rating Scale for Depression[8] (HRSD) scores of 12 or higher, previously completed an 8-week trial of duloxetine monotherapy (60–120 mg daily). Five of these subjects failed to achieve clinical response as measured by a reduction of 50% or greater in HRSD. These subjects, who had been sexually active in the previous month, also reported moderate treatment emergent sexual dysfunction as measured by the Sex Effects questionnaire (SEX-FX).[9] This subgroup of patients (mean age, 41.8 years; Table 1) then received mirtazapine 30 mg daily in combination with duloxetine (60–90 mg) for a further 8 weeks with an option to increase or decrease the mirtazapine dose by 15 mg after the first 4 weeks. The primary end point was change in SEX-FX; and secondary end point, the change in HRSD over the 8 weeks of mirtazapine add-on therapy. Results were analyzed using paired-sample *t* tests.

All patients completed the 8-week treatment. Although there was no statistically significant improvement in SEX-FX scores over time, 2 of the patients did achieve a significant improvement, and the other 3 reported no further decreases in sexual functioning. The combination of medications was well tolerated, with no reported side

TABLE 1. Demographics and Clinical Characteristics

Subject/Age	$HRSD_B$/$HRSD_E$	$SEX\text{-}FX_B$/$SEX\text{-}FX_E$	Duloxetine Dose at End Point (mg)	Mirtazapine Dose at End Point (mg)
M_1/39	18/18	4/4	90	45
M_2/55	16/9	9/26	60	30
F_1/28	12/4	11/33	60	15
F_2/47	13/5	11/12	60	30
F_3/40	14/8	36/37	60	15

F, female; $HRSD_B$, HRSD scores at baseline; $HRSD_E$, HRSD scores at end point; M, male; $SEX\text{-}FX_B$, SEX-FX scores at baseline; $SEX\text{-}FX_E$, SEX-FX scores at end point.

effects apart from weight gain (2.3 ± 1.48 kg). At end point, mean doses of medications were duloxetine 66 (±12) mg and mirtazapine 27 (±11.2) mg. There was a significant decrease in the mean HRSD score after 8 weeks of treatment ($P = 0.018$), with 4 patients achieving response, of which, 2 met criteria for remission (HRSD, ≤7).

DISCUSSION

The combination of duloxetine and mirtazapine seems to be a helpful and well-tolerated pharmacological strategy to enhance antidepressant response and sexual function. It is difficult to conclusively state whether the improvement in depressive symptoms or the mechanism of action of mirtazapine was responsible for improved sexual function. One way to clarify the issue might have been to add mirtazapine to responders with treatment-emergent sexual dysfunction in the original duloxetine monotherapy study. Nevertheless, the role of mirtazapine as a potential antidote to antidepressant-induced sexual dysfunction is well documented,[6,7,10,11] although there are no double-blind trials to date. Mechanisms posited to explain mirtazapine's effectiveness in this respect include antagonism of $5HT_{2a/2c}$, $5\text{-}HT_3$, and $\alpha2$-adrenergic receptors.[12] Notably, $\alpha2$-adrenergic blockade has been shown to enhance erectile function.[13] These results provide initial support for further evaluation of the therapeutic and tolerability benefits of combining duloxetine and mirtazapine under randomized double-blind conditions.

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High-Dose Escitalopram Treatment in Patients With Obsessive-Compulsive Disorder

A Naturalistic Case Series

To the Editors:

Obsessive-compulsive disorder (OCD) is a chronic illness that causes considerable disability. Serotonin reuptake inhibitors (SRIs), the first-line treatment for OCD, are effective in only about half of patients with OCD, and many responders still have marked residual symptoms.

Two features are known to be different between the ways in which SRIs are used to treat OCD versus depression. First, higher dosages of SRIs are usually required to achieve a response in OCD compared with depression. Second, the delay between treatment initiation and response to SRIs is longer in OCD (10–12 weeks) than in depression (2–6 weeks).[1,2] For these reasons, Dougherty et al[1] recommended that a high therapeutic dosage should be targeted during the initial dosage escalation, with the up-titration limited principally by side effects and that after a satisfactory therapeutic response has been achieved, some tapering of the dosage can be attempted to determine the lowest effective dosage for the individual patient.

Several case reports have suggested that some patients who do not respond to standard therapeutic doses might respond to much higher doses.[3–5] Furthermore, among the subjects who did not respond to 16 weeks of sertraline at 50 to 200 mg/d, continuation treatment with high-dose sertraline (250–400 mg) resulted in significantly greater and more rapid improvement in OCD symptoms

than that seen with the maximum dose of sertraline (200 mg) in a multicenter double-blind trial.[6]

Escitalopram (SCTP), the therapeutically active S-enantiomer of racemic citalopram, is a potent and highly selective SRI. The adverse events profile for SCTP is similar to that observed with RS-citalopram in both major depressive disorder and anxiety disorders.[7] Discontinuations due to adverse events were similar in patients treated with SCTP and placebo in several well-designed trials.[8–11]

To investigate the effectiveness and tolerability of high-dose SCTP therapy in OCD, we reviewed the medical charts of patients with OCD who had been administered high-dose SCTP. A consecutive series of 20 outpatients and 1 inpatient, aged 17 to 56 years, were included. During the SCTP treatment period, all subjects were scheduled to receive more than 20 mg SCTP daily if tolerated. Patients with another primary Axis I psychiatric diagnosis were not excluded from this study, but all patients were required to have scores of 4 or higher on the Clinical Global Impression–Severity (CGI-S) scale[12] and to experience more discomfort and impairment from the OCD than from another disorder.

All eligible patients were administered SCTP without a structured protocol; there was no mandated dosing schedule. The maximum SCTP dosage did not exceed 80 mg/d. All patients took SCTP with or without combined medication.

The severity of a patient's illness was assessed with the CGI-S scale at the time SCTP treatment was initiated, at the time the SCTP dose reached 20 mg, and at the final observation point. The response to treatment was assessed using the CGI-Improvement (CGI-I) scale[12] at the time the SCTP dose reached 20 mg and at the final observation point. In this study, the CGI-S and CGI-I scores were retrospectively rated by 1 investigator based on clinical documentation in the electronic medical records. The primary efficacy measure was defined as the number of responders with a CGI-I score of 1 or 2 ("very much improved" or "much improved") after SCTP high-dose therapy.

A total of 21 patients (17 men and 4 women) with a mean age of 27.6 ± 9.7 years and mean duration of illness of 9.3 ± 6.1 years were classified into 3 groups according to previous treatment history. Group 1, the drug-naive group, comprised 2 subjects who had not taken any psychiatric medicine before the SCTP trial. Group 2, the poor compliance group, included 6 subjects. All 6 subjects had received anti-OCD medication before the SCTP trial. Five of the 6 subjects had not taken any psychiatric medicine for several months before the SCTP trial because of adverse events or unsatisfactory treatment outcome. One of the 6 subjects had taken an anti-OCD drug irregularly before the SCTP trial, which had led to insufficient pharmaco-

therapy and resulted in the only admission to a psychiatric ward during the study. Group 3, the SRI-resistant group, consisted of 13 subjects who had been given full doses of more than 1 SRI. Despite sufficient time for a response to be seen before the SCTP treatment, all 13 subjects had shown an insufficient treatment response, with CGI-S scores of 4 or higher.

The mean observation period was 143.6 ± 46.4 days, and the mean time to the evaluation of the CGI-S and CGI-I scores at the administration of 20 mg SCTP was 33.0 ± 28.6 days from the initiation of the SCTP trial. The mean period that each patient took a dosage of 20 mg/d SCTP before proceeding to a higher dosage was 38.8 ± 43.1 days, and the mean dose-titration period from initiation to 30 mg/d SCTP was 46.0 ± 45.4 days. The mean maximum SCTP dosage was 41.9 ± 13.5 mg/d. Only 1 patient received an SCTP dose of 25 mg or less throughout the study, and this was attributable to adverse events.

The mean CGI-S scores at the 3 assessment points, given in Figure 1, were significantly different ($P = 0.029$; Kruskal-Wallis test). At the end point, the mean CGI-I score was 2.6 ± 1.1. Based on the CGI-I scores, 4 (19%) and 6 (29%) of the 21 patients were "very much improved" and "much improved" at the end point. Only 2 patients responded while taking 20 mg SCTP, and 3 of the 4 patients who received cognitive behavioral therapy were responders. The relatively low responder rate of this study can be attributed to the relatively strict definition of "responders," which did not include "minimally improved" patients after SCTP therapy. Additionally, SRI-refractory patients had a greater chance of being recruited in our study. The 13 SRI-resistant patients included in our study showed a response rate of 38.5%. On the other hand, the remainder of the subjects, the drug naive and poor compliance groups, exhibited a combined response rate of 62.5%. If 1 patient, who received less than 25 mg SCTP throughout the study, was excluded, the response rate of Groups 1 and 2 became 71.4%.

In our study, 11 (52.4%) and 14 (66.7%) of the 21 patients reported at least 1 treatment-emergent adverse event during recommended dose and high-dose SCTP treatment; however, most of the
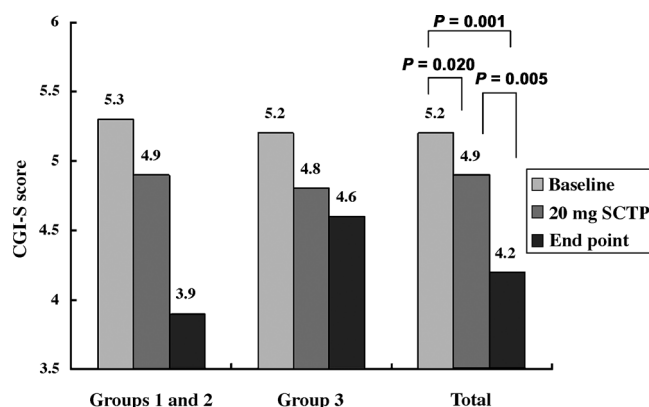

FIGURE 1. The mean CGI-S scores at the 3 assessment points were indicated separately: the drug-naive and poor compliance groups (Group 1 and 2), the SRI-resistant group (Group 3), and all 3 Groups. The mean CGI-S score change between baseline and end point in Group 3 was less than that in Groups 1 and 2, but no statistically significant difference was found ($P = 0.104$, Mann-Whitney U test). As indicated with P values above the bar graph, significant changes in the CGI-S scores for all 3 possible combinations of assessment points were detected (Wilcoxon signed rank test).

events were mild to moderate. Sedation or somnolence was the most common adverse event recorded at an SCTP dose of 20 mg or less (47.6%) and after high-dose SCTP treatment (42.9%). Considering that nausea or headache was the most common adverse events in SCTP recipients in other studies,[9,11,13,14] combined medications such as antipsychotics and benzodiazepines might have contributed the side effect profile in our study. As a notable side effect, 1 patient showed mood elation 4 days after 30mg/d SCTP medication. Rapid titration of a selective serotonin reuptake inhibitor has a potential risk of inducing mood elation in a patient with bipolarity. However, in our study, the subject's elated mood was not aggravated with a further increase of SCTP dose and more stabilized at the end point. Three patients were intolerant of the maximum dose of SCTP; 2 patients reported excessive sedation, and 1 patient exhibited abnormalities on the liver function tests, which were nearly normalized after the SCTP dose was reduced.

The retrospective design of our study limits the blinding of the outcome assessor. Despite the limitation, we found that SCTP doses higher than that recommended for patients with major depressive disorder are well tolerated and effective for the treatment of OCD. Additional studies, including a double-blind case-controlled trial, are necessary to validate our results and assertions.

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Six-Month Randomized, Placebo-Controlled, Double-Blind, Pilot Clinical Trial of Curcumin in Patients With Alzheimer Disease

To the Editors:

Curcumin is a polyphenolic molecule that comprises approximately 5% of turmeric, giving the spice its color but not flavor. It is used in processed foods as a yellow coloring.[1] Because of its anti-inflammatory and antioxidant properties, curcumin has been tested in animal models of Alzheimer disease (AD). In the Tg2576 APPSw mouse and amyloid-infused rat models of AD, 6 months of an oral dose equivalent (as a proportion of body weight) to roughly 1.5 g/d in humans significantly reduced levels of brain amyloid, plaques, oxidized proteins, and isoprostanes and prevented cognitive deficits in the rat model.[2,3] Elderly Singaporeans who ate curry with turmeric had higher Mini-Mental State Examination (MMSE) scores than those who did not.[4] Because no study has been published on the effect of curcumin on human AD patients, we performed a 6-month clinical trial of curcumin to examine its safety and effects on biochemical and cognitive measures in AD.

There are no ideal AD biomarkers. Amyloid β (Aβ) levels were higher in blood of AD patients than controls in some studies but not others.[5] Curcumin can disaggregate Aβ, and AD drug treatment may affect Aβ levels.[6–8] Blood isoprostanes were increased in AD versus controls in some studies but not in others, whereas antioxidants were decreased.[9–11] As an antioxidant,[1–3] curcumin might relieve the load on other antioxidants. Thus, we measured serum Aβ and plasma isoprostanes and antioxidants. Because curcumin has low oral bioavailability,[12] we also measured plasma curcumin and its metabolites.

Patients were eligible for this double-blind, placebo-controlled, randomized, 6-month trial if they were 50 years old or older, ethnic Chinese in Hong Kong, had progressive decline in memory and cognitive function for 6 months, had National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association diagnosis of probable or possible AD,[13] and gave written informed consent. For subjects unable to understand the study and their role in it, consent was obtained from the caregivers. Exclusion criteria were anticoagulant or antiplatelet treatment or bleeding risk factors, current smoking, or severe illness making study completion unlikely. The study was

approved by the Hong Kong Clinical Research Ethics Committees for New Territories East and Kowloon West and followed the Helsinki Declaration. Thirty-four patients were recruited: 9 from old age homes and 24 from dementia clinics. When the trial period was nearing conclusion, 2 additional patients were recruited but could only be treated and monitored for 1 month. Patients were randomized to 4, 1 (plus 3 g color-matched placebo powder), or 0 g of curcumin (plus 4 g of placebo) once daily, with stratification by their prestudy Cantonese MMSE[14] score range (<14, 14–17, or >17) to improve matching of baseline scores among dose groups. Of 22 patients randomized to 4 or 1 g, 10 patients chose to take curcumin/placebo as 10 capsules to swallow after a meal; and 12 patients, as a packet of powder to mix with food. Patients were permitted to continue (or to change at any time) any treatment deemed appropriate by their physicians and were also given as a standard treatment, which showed moderate benefit in previous studies, 1 capsule/d 120 mg standardized ginkgo leaf extract (Shanghai Charoma, Shanghai, China).[15] Curcumin was given by Kancor Flavours, Kerala, India, for packets, or bought from Arjuna Natural Extracts, Kerala, India, for capsules.

At 0, 1, and 6 months, plasma was taken to measure isoprostanes $iPF_{2\alpha}$-III and antioxidants, and so was serum to monitor $A\beta$ and liver and kidney function. At 1 month, plasma was taken to assay curcumin and metabolites. Mini-Mental State Examination was administered at baseline and 6 months. Amyloid β_{40} was measured by enzyme-linked immunosorbent assay (Covance, Dedham, Mass). Curcumin is a mixture of 3 similar molecules—curcumin, demethoxycurcumin, and bisdemethoxycurcumin (CDB), the former being most abundant. Curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin, ferulic acid, vanillic acid, and vanillin were measured in plasma by liquid chromatography–mass spectrometry-mass spectrometry[12] after β-glucuronidase treatment (Sigma, St Louis, Mo). To measure isoprostanes, blood was collected in lithium-heparin tubes with 15 μM of indomethacin. Butylated hydroxytoluene was added to

plasma to 20 μM. Isoprostanes were enriched by an affinity column and measured by gas chromatography–mass spectrometry. High-performance liquid chromatography assays measured antioxidants: plasma glutathione peroxidase and superoxide dismutase activity, ascorbic acid, uric acid, and vitamins A and E.[16,17] Statistics were calculated using SPSS 11.5 (SPSS Inc, Chicago, Ill). Continuous variables were compared by testing for normality (Kolmogorov-Smirnov test) and then analysis of variance or *t* test for normal distributions and Wilcoxon or Mann-Whitney *U* test otherwise. Discrete variables were compared using χ^2 test.

Thirty-four subjects began the 6-month trial. Of 27 finishing it with less than 30 cumulative days off the study drug (8 subjects on 0 g, 8 on 1 g, and 11 on 4 g), baseline clinical measures were matched across dose groups: ages (mean ± SD) were 77.8 ± 7.7 years on 0 g, 69.0 ± 10.9 on 1 g, and 73.4 ± 6.6 on 4 g ($P = 0.14$); male subjects were 3 of 8 on 0 g, 1 of 8 on 1 g, and 3 of 11 on 4 g ($P = 0.52$); and MMSE scores (mean ± SD) were 15.4 ± 5.8 on 0 g, 15.4 ± 5.0 on 1 g, and 15.6 ± 7.9 on 4 g ($P = 1.0$). Of the other 7 subjects, 0 were on 4 g/d curcumin, 3 on 1 g, and 4 on 0 g ($P = 0.11$); 3 withdrew for gastrointestinal complaints, 3 for falls or dizziness, and 1 for respiratory tract infection. To monitor safety, sodium, potassium, urea, creatinine, protein, albumin, bilirubin, alkaline phosphatase, and alanine aminotransferase/glutamic-pyruvic transaminase were measured, but any toxicity not affecting these values might have been missed. Changes in none of the values between baseline and 6 months differed significantly among dose groups. Adverse events totaled 7 on 0 g, 6 on 1 g, and 2 on 4 g: 4 gastrointestinal (2 on 0 g, 2 on 1 g, and 1 on 4 g), 3 respiratory tract infections (2 on 0 g and 1 on 1 g), 3 falls or dizziness (1 on 0 g, 1 on 1 g, and 1 on 4 g), 2 delusional (1 on 1 g and 1 on 4 g), 2 edema (1 on 0 g and 1 on 1 g), and 1 hearing impairment (on 0 g). Power was 14% to detect an α of 0.05 difference between curcumin and 0 g in MMSE changes of the same effect size as a 24-week donepezil study.[18]

Changes in MMSE scores between 0 and 6 months were compared among dose groups, either including

(mean ± SE, 1.3 ± 0.6 on 0 g; −0.6 ± 1.0 on 1 g; and 0.7 ± 1.1 on 4 g; $P = 0.43$) or excluding ($P = 0.37$) patients on vitamin E or standard AD drugs, and between 0 g and curcumin (mean ± SE, 1.3 ± 0.6 on 0 g; 0.2 ± 0.7 on curcumin; $P = 0.39$) for patients using capsules (mean ± SE, 1.5 ± 0.7 on 0 g, −0.2 ± 1.3 on curcumin; $P = 0.34$) or packets (mean ± SE, 0.0 ± undefined on 0 g; 0.5 ± 0.8 on curcumin; $P = 0.86$). Serum $A\beta_{40}$ levels (Fig. 1) did not differ among doses at 0 ($P = 0.63$), 1 ($P = 0.78$), or 6 months ($P = 0.36$). Between baseline and 6 months, serum $A\beta_{40}$ (mean ± SE) changed from 30 ± 6 ng/L to 26 ± 3 on 0 g and from 28 ± 6 to 35 ± 7 on 4 g ($P = 0.15$). The change in serum $A\beta_{40}$ between baseline and 1 month did not differ between patients taking curcumin as capsules (mean ± SE, 26 ± 18%) or powder (mean ± SE, 27 ± 22%; $P = 0.66$). The change in plasma isoprostanes (mean ± SE) between baseline and 6 months did not differ among doses ($P = 0.23$): −11 ± 10% for 0 g, 12 ± 10% for 1 g, and 6 ± 8% for 4 g. The change in isoprostanes between baseline and 6 months did not differ between patients taking curcumin as capsules (mean ± SE, 15 ± 7%) or powder (mean ± SE, 4 ± 9%; $P = 0.43$). Over 1 month, vitamin E levels changed, 1 ± 3% with curcumin (8 ± 2% for capsules vs −4 ± 5% for powder; $P = 0.05$) versus −21 ± 5% with 0 g ($P = 0.001$), and the percent change of vitamin E levels correlated positively with the total curcuminoid level ($P = 0.01$; Pearson correlation); patients taking vitamin E supplements were excluded.

In a preliminary experiment, curcumin was measured in plasma from 1 nondemented control subject at various times after 4 g of curcumin either with or without food. No signal was detected unless the plasma was first treated with glucuronidase, demonstrating that nearly all the curcumin was glucuronidated. The level of curcumin (CDB) peaked at 250 nM at 1.5 hours with food and at 270 nM at 4 hours with only water. At 24 hours, the level fell to 60 nM. Based on these findings, we decided to measure curcumin 2 to 2.5 hours after ingestion. There were no significant differences in levels of any curcuminoids or of total curcuminoids between 1- and 4-g groups; thus, both groups

were pooled for calculating mean ± SE (in nanomolar) levels: 250 ± 80 curcumin, 150 ± 50 demethoxycurcumin, 90 ± 30 bisdemethoxycurcumin, 440 ± 100 tetrahydrocurcumin, 110 ± 20 ferulic acid, 50 ± 20 vanillic acid, 490 ± 160 CDB, and 1100 ± 260 total curcuminoids. No vanillin was detected in any samples. One patient receiving 1 g/d had total curcuminoid levels 2.8 times as high as any other patient, and when this patient was excluded, total curcuminoid levels tended to be greater with 4 g than with 1 g ($P = 0.15$): 1040 ± 150 versus 650 ± 210. Patients taking capsules (taken fasting with water; 10 patients) had greater levels of CDB than did patients taking powder (with a little food; 12 patients): 940 ± 290 versus 120 ± 40; $P = 0.02$. However, levels of tetrahydrocurcumin, ferulic acid, or vanillic acid did not differ between patients on capsules or powder.

DISCUSSION

As the first study published on curcumin treatment of AD patients, this trial provided data on side effects, drug absorption, and biological effects. Curcumin may act in AD by several possible mechanisms, including $A\beta$ disaggregation, anti-inflammation, and antioxidation.[2,3,7,8,19] The lack of cognitive decline on placebo in this 6-month trial may have precluded any ability to detect a relative protective effect of curcumin, which presumably would have appeared as a slower decline rather than an improvement in cognition. A study of longer duration, with a more sensitive test such as the Alzheimer Disease Assessment Scale–cognitive subscale and perhaps less treatment by other AD drugs, may show greater deterioration on placebo.

The greater level of curcumin but not tetrahydrocurcumin, ferulic acid, or vanillic acid after capsules than powder may be due to more absorption and less metabolism of curcumin from capsules, suggesting that capsules be used in future trials. The lack of difference in curcumin or metabolite levels between 1- and 4-g groups suggests that there may be no need to exceed 1 g in future trials. Curcumin prevents or reverses half of the aggregation (IC_{50}) of $A\beta$ at 0.2 to 1 μM CDB.[7,8] In this study, mean plasma CDB was 490 nM (940 nM for capsules). A study in mice found that curcumin reached similar concentrations in the brain as in plasma: 0.41 μg/g in brain and 0.60 μg/g in plasma.[12] Thus, curcumin may reach brain concentrations sufficient to decrease $A\beta$ aggregation. Metabolites of curcumin might contribute further; the IC_{50} of ferulic acid is 2 to 10 μM, and tetrahydrocurcumin has not yet been tested.[20]

Plasma antioxidants, including glutathione peroxidase and superoxide dismutase activity; uric acid; and vitamins A, C, and E, were reportedly decreased in AD.[11] We found that curcumin raised vitamin E. One interpretation is that the antioxidant activity of curcuminoids might decrease need for and depletion of the antioxidant vitamin E. Another possibility is that curcumin slows AD progression, reducing oxidation because of processes within the AD brain.

Although serum $A\beta_{40}$ levels did not differ significantly among doses, serum $A\beta_{40}$ tended to rise on curcumin, possibly reflecting an ability of curcumin to disaggregate $A\beta$ deposits in the brain, releasing the $A\beta$ for circulation and disposal.[7,8]

Curcumin did not seem to cause side effects in AD patients (rather, there was a tendency toward fewer adverse events on 4 g). Thus, longer and larger trials to test the efficacy of curcumin for treating AD may be safely commenced.

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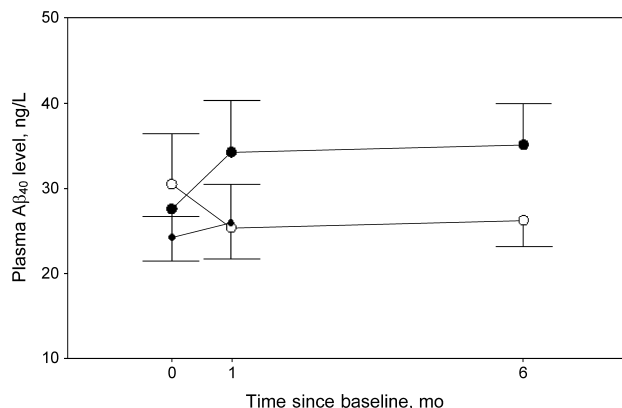**Iris Hiu Shuen Chan, PhD†**
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FIGURE 1. Mean ± SE plasma $A\beta_{40}$ levels in dose groups among subjects completing the 6-month study: placebo (open circles), 1 g/d curcumin (small closed circles), and 4 g/d curcumin (large closed circles).

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Suanzaorentang and Serotonin Syndrome

To the Editors:

In Asia, traditional Chinese medicine has a long history of use, and many over-the-counter (OTC) drugs in Asian countries are made up of Chinese herbal agents. Chung and Lee[1] in 2002 did a cross-sectional survey of OTC sleeping pills at drug stores in a small district of Hong Kong with 0.3 million population. The Chinese herbal mixture suanzaorentang was the most common OTC sleeping pill used. It contains *Zizyphi spinosi* semen, *Poria cocos*, *Ligusticum wallichii*, *Anemarrhenae rhizome*, and *Glycyrrhizae radix* in ratio of 7:5:2:1:1.

The ancient Chinese remedy suanzaorentang was originally described in Kin-Kue-Yao-Lueh for patients with weakness, irritability, and insomnia. It is found to be of significant benefit in treating anxiety and insomnia.[2–4] Adverse reaction was not systematically examined, and there were occasions of mild side effects such as gastrointestinal symptoms, dizziness, and skin rash only.[2,3] However, there is a report of severe drug interaction between suanzaoren with venlafaxine where the patient presented with agitation, restlessness, profuse diaphoresis, ataxia, widely dilated pupils, and cardiovascular collapse.[5] It is compatible with serotonin syndrome (SS).[6] Further search from Chinese literature reveals a report of severe diaphoresis and restlessness after taking a high dose of suanzaoren.[7] There were not enough details to judge whether it is compatible with mild SS. The patients in all 3 cases recovered within a day.

Among Western herbal drugs, St John's wort has been reported with a few incidents of suspected SS.[8] Ayahuasca, used in Amazonian with potent monoamine oxidase-inhibiting activity, can lead to SS in combination with selective serotonin reuptake inhibitors.[9,10]

Serotonin syndrome, a potentially fatal adverse drug reaction, is more common now that the drugs that have an impact on the serotonergic system are increasingly prescribed, either alone or in combination. Another reason may be related to its enhanced recognition in recent years. Moreover, a wider availability of drugs affecting the cytochrome P450 enzymes (especially CYP2D6 and CYP3D4) that results in increased propensity for drug interactions impacting the serotonergic system may also be to blame. A single therapeutic dose of a selective serotonin reuptake inhibitor has been known to cause SS. However, most incidents of the severe manifestations of SS have been precipitated by drug combinations.

To reach a diagnosis of SS, a history of use of a serotonergic agent, recognized signs and symptoms, and the exclusion of other conditions are required. Successful management relies upon prevention, early recognition, and supportive care. Serotonin syndrome usually resolves within 24 to 48 hours after discontinuation of offending medications.

The difficulty for a clinician is that mild symptoms may be overlooked, and an inadvertent increase in the dose of the causative agent or the addition of a drug with proserotonergic effects may provoke a dramatic clinical deterioration. It is important for clinicians to ask

all patients about use of herbs and provide education about potentially dangerous drug-herb interaction.

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Trapped in the "K-hole"
Overview of Deaths Associated With Ketamine Misuse in the UK (1993–2006)

To the Editors:

Ketamine is a noncompetitive glutamate *N*-methyl-d-aspartate receptor antagonist. Although used as a general anesthetic primarily in veterinary practice, it is occasionally administered to humans as well.[1] Recreational use of ketamine started during the early 1970s in California and, during the 1990s, ketamine was initially sold in the UK as "ecstasy."[2] A self-selected readers' survey of a magazine aimed at clubbers found that during the period 1999 to 2003, ketamine lifetime prevalence in the UK increased from 25.5% to 39.8%, whereas current use increased from 3.9% to 16.0%.[3] When misused, ketamine can be injected, sniffed, or smoked. At low doses, ketamine stimulant effects predominate. With higher doses, its psychotropic effects range from referential thinking, dissociation, and depersonalization to psychotic experiences and include a sensation of feeling light, body distortion, absence of time sense, novel experiences of cosmic oneness, and out-of-body experiences, often called the "K-hole."[4] Due to its sympathomimetic activity, ketamine causes mild stimulation of the cardiovascular system, pupil dilation, and bronchodilation and does not suppress respiration and gag reflex. Due to these characteristics, ketamine use in medical and veterinary settings has a good safety record. Conversely, administration of the drug in high doses can cause cardiovascular and respiratory toxicity,[1] and the increase in its unregulated use outside controlled environments may be a cause for concern. In fact, recreational ketamine users may experience numbness of the limbs, analgesia, change in the body temperature, and vomiting. There is a risk that the user can choke on his vomit. Difficulty with balance, combined with numbness, muscle weakness, and impaired perception can result in falls, trauma, or burns.[5] Risks from the setting have also included drowning, death by hypothermia from lying outside in winter, traffic accidents, and becoming a crime victim (eg, "date rape"[1,5,6]). Despite the reported increased use of ketamine as a recreational drug, relatively few reports of fatalities attributed to ketamine poisoning, either alone or in combination, have been documented. Gill and Stajic[7] reviewed 87 ketamine-positive deaths occurring in New York City during a 2-year period (1997–1999), but only 12 were nonhospital deaths due to acute polydrug misuse intoxications. In no instance was a fatal intoxication caused exclusively by ketamine. Between 1978 and 1997, the Institute of Legal Medicine in Hanover, Germany, examined 17 fatal autoerotic deaths, all involving males with an average age of approximately 37 years. Apart from ketamine, other compounds identified at postmortem included alcohol, chloroform, and a propane-butane gas mixture.[8]

Because of the paucity of ketamine misuse mortality data, the aim of this report was to focus on those figures that were available for the UK (1993–2006). To gather together all the available ketamine misuse mortality figures, 2 different approaches were combined: (a) data were extracted from the National Programme on Substance Abuse Deaths (np-SAD) database, St George's, University of London for the time frame July 1997 to December 2006; (b) data based on drug-poisoning mortality statistics published by the General Register Offices (GROs) for England/Wales and Scotland were collected, together with data provided to the np-SAD by the GRO for North Ireland from January1993 to December 2006. Since its inception, the np-SAD has been regularly receiving coroners' information on drug-related deaths among both addicts and nonaddicts in the UK. To be recorded in the np-SAD database, cases must meet one or more of the following criteria: presence of one or more psychoactive substances directly implicated in death; history of dependence or abuse of psychoactive drugs; and presence of controlled drugs at necroscopic examination. The coroners' response rate has been estimated to have been as high as approximately 90% to 95%.[9] Ketamine-related deaths were defined here as: "text search identified ketamine written in the coroner's report (other illegal drugs may also be written)." Data from np-SAD were not included in the total number of cases derived from other records. Cases where ketamine was present as a result of being administered for medical reasons were excluded from this study.

We identified 23 deaths in the UK during the period 1993 to 2006 where ketamine was mentioned, either on the death certificate or in the np-SAD coroners' report. Eighteen cases were notified directly to the np-SAD, and a further 5 cases were identified from GRO sources (Table 1). Aggregating the information for these 2 sources of data, we found that these deaths mostly occurred in the 1999 to 2006 time frame, with numbers increasing over time. Most victims were males (19/23) and in the 25 to 44 age group; 21 cases

TABLE 1. Summary Results for 23 Ketamine Cases Notified to Either the np-SAD (18 Fatalities) or the GROs Occurring in the UK (1993–2006)

Year of death	1999: 2; 2000: 2; 2001: 1; 2002: 3; 2003: 1; 2004: 2; 2005: 4; 2006: 3
Gender and age, y	Male = 16; Female = 2; Average age = 32.74; Range = 19.8–49.4
Drug abuse history	Yes = 13; No = 2; Not known = 3
Prescribed medication	Yes = 6 (including methadone in 1 case and diazepam in 2 cases); No = 6; Not known = 6
Incident site	Home/other specified residential place = 10; industrial site = 1; place of recreation = 1; river = 1; not known = 5
Cause(s)/Mechanisms of death	Ketamine and methadone toxicity
	Bronchopneumonia, hypoxic brain damage, cardiorespiratory arrest due to drug toxicity
	Combined GHB, amphetamine, and ketamine toxicity
	Drug abuse, bronchial asthma
	Drug overdose (morphine and ketamine)
	Ketamine and alcohol poisoning
	Opiate poisoning
	MDMA and ketamine overdose
	Drowning
	Complications of mixed drug intoxication, due to ingestion of alcohol, cannabis, ketamine, diazepam, MDMA, and heroin, followed by prolonged unconsciousness
	Stab wound to chest
	Pulmonary edema, cardiac arrhythmias, and drug intoxication
	Heroin poisoning
	Cerebral and pulmonary edema, mixed drug poisoning
	Cerebral and pulmonary edema, cocaine intoxication
	Respiratory depression, multiple drug poisoning
	Ketamine toxicity
	Ecstasy, ketamine, and GHB toxicity
Drugs present at postmortem	Alcohol, methadone, and ketamine
	Ecstasy, morphine/diamorphine, opiates, ketamine, and benzodiazepines
	Amphetamine, ketamine, ecstasy, cannabis, and GHB
	Alcohol, amphetamines, and ketamine
	Ethanol, ketamine, and morphine
	Alcohol, ketamine, and cannabis;
	Morphine, ketamine, cocaine, and codeine
	MDMA and ketamine
	Diazepam, ethanol, ketamine, temazepam, opiate-type, and substance
	Alcohol, cannabis, ketamine, diazepam, MDMA, and heroin
	Ketamine only (×2)
	Ecstasy, ketamine, and ephedrine
	Heroin, ketamine, and temazepam
	Ethanol, cocaine and metabolites, ketamine, and morphine
	Cocaine and metabolites, diazepam and metabolites, ketamine, and cannabinoids
	MDMA, MDA, methylamphetamine, ketamine, amphetamine, cocaine and metabolites, and cannabis metabolites
	Ecstasy, ketamine, cocaine, and GHB
Circumstances of death	While drinking with others (×2); while clubbing with others; injecting with partner; snorted while with others; collapsed during illegal rave; drowned; taken before killing himself with a knife; took with a range of other stimulants before engaging in gay sex with group of new acquaintances; overheated while wearing rubber body suit; took to excess trying to calm herself down; consumed range of drugs during a period of 2 days at various gay venues. Not known = 6
Verdict	Accident/misadventure = 11; open = 2; suicide = 1; dependent abuse of drugs = 1; abuse of drugs = 1; nondependent abuse of drugs = 1; self-administered overdose of drugs = 1
Additional cases from GRO sources (1993–2006)	*England & Wales–ONS data*: 3 deaths of accidental poisoning (1993–2002); 2 males and 1 female; ages within the range 20–49 years. Drugs mentioned: 2× ketamine alone; 1 ketamine + coproxamol. *Scotland (1994–2006)*: a 26-year-old woman, died in 1997. Cause of death recorded as septic shock, buttock abscess, and chronic drug abuse. Drugs identified: ketamine, lignocaine, diazepam, temazepam, morphine. *Northern Ireland (1997–2005)*: a 35-year-old man, died in 2001. Cause of death recorded as aspiration of vomit and poisoning by ketamine, temazepam, and alcohol.

GHB indicates gamma-hydroxybutyrate; MDA, methylenedioxyamphetamine; MDMA, methylenedioxymethamphetamine.

were recorded in England and Wales. At postmortem toxicological examination, ketamine was detected in 4 cases on its own. For these cases, poisoning was the cause of death in all cases, and the coroner's verdict was accidental in 3 cases and suicide in 1 case. In the remaining victims, alcohol (8 cases), opiates/opioids (10 cases), benzodiazepines (7 cases), and cocaine (6 cases) were mostly identified here in conjunction with ketamine. Most (13/18) of the subjects notified to the np-SAD were known as drug addicts.

DISCUSSION

To the best of our knowledge, the present report constitutes the largest available collection of ketamine *misuse* mortality data from both the UK and elsewhere. In this report, we described 4 cases where ketamine was detected on its own, somewhat questioning the ketamine high-safety profile suggested elsewhere.[10] One could argue, however, that these 4 cases were possibly related to enhanced likelihood of accidents caused by some level of misjudgment of risk, which was in turn associated with ketamine dissociative effects. One might wonder if the real cause of death, in polydrug cases, was due to a particular pharmacokinetic interaction and/or to a synergistic effect of the different self-administered drugs. A possible limitation of the present study is given by our definition of ketamine "related" deaths, which was as comprehensive as possible. The fact that a drug was recorded as being present postmortem does not necessarily imply that it contributed directly to the death. Furthermore, changes in coroners' reporting over time cannot be excluded here. Postmortem toxicological screens are carried out in only approximately 2 of 3 cases of accidental deaths in the UK.[2,9] Furthermore, ketamine is routinely screened for in toxicology tests only in a number of highly specialized laboratories and/or upon specific request. It is here suggested that coroners and procurators fiscal should be encouraged to consider more routine screening for recreational drugs, including ketamine, in unexpected deaths.

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Methylphenidate and Depression

To the Editors:

I read with interest the placebo-controlled trial by Patkar et al[1] on augmentation with extended release methylphenidate in an outpatient population with treatment-resistant depression. There seems to be a renewed interest in the use of stimulants as an augmentation agent in depressive disorders, with several trials in recent years, including the elderly population[2] and the possible use of newer agents such as modafinil.[3,4] Fatigue, tiredness, and excessive sleepiness are common symptoms in presentation, which may be exacerbated, or not be treated, by standard antidepressants.[5]

The authors raised 3 possible reasons why extended-release methylphenidate did not separate from placebo on the efficacy measures—the strategy has a low efficacy in treatment-resistant depression, a high placebo response, or a possible type II error. Another possibility is that the trial's population may have had few or low levels of fatigue, apathy, hypersomnia or psychomotor retardation, and potential target symptoms of stimulant augmentation, leading to a failure to separate efficacy of extended-release methylphenidate over placebo.

Two recent trials of modafinil specifically measured sleepiness and fatigue as efficacy measures.[3,4] One study also noted no significant differences between adjunct modafinil and placebo on Hamilton Depression Rating Scale scores or on any of the scale's individual items. However, there was a nonsignificant trend favoring modafinil on the psychomotor retardation item.[3] Are the authors able to provide any analysis on whether there were any significant differences in change on individual scores on the Hamilton Depression Rating Scale, particularly retardation and general somatic symptoms, or on the Beck Depression Inventory II, which rates loss of energy, changes in sleeping pattern, and tiredness?

The article also did not detail the number of patients on each specific antidepressant. Was analysis possible for potential differences on any of the efficacy measures between classes of

antidepressants (eg, serotonin reuptake inhibitors vs serotonin-norepinephrine reuptake inhibitors vs tricyclic antidepressants)?

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Reply to Dr Ng's Comments on "A Randomized, Double-Blind, Placebo-Controlled Trial of Augmentation With An Extended Release Formulation of Methylphenidate in Outpatients With Treatment-Resistant Depression"

To the Editors:

We appreciate Dr Ng's comments on our recent publication entitled "A Randomized, Double-Blind, Placebo-Controlled Trial of Augmentation With An Extended Release Formulation of Methylphenidate in Outpatients With Treatment-Resistant Depression."[1] As he pointed out, the use of stimulants as an augmentation agent in depressive disorders has been conducted through several randomized placebo-controlled clinical trials.[2,3]

Several possible neural pathways and neurotransmitters such as dopamine may be related to the development of fatigue or decreased energy in major depression, although precise mechanisms have not yet been clearly understood. In an animal study, dopamine depletion in the nucleus accumbens was found to reduce motivation and psychomotor retardation.[4] The ventral striatum and prefrontal cortex are believed to be important dopaminergic regions involved in motivation.[5] Specifically, reduced neuronal activities in the dorsolateral prefrontal cortex, which is well known as executive center, have been supposed to be associated with fatigue/energy-related symptoms.[6,7] Comprehensive and multidimensional researches will considerably facilitate the understanding of fatigue/decreased energy in major depression, resulting in enhanced knowledge about the role of psychostimulants for treating those carrying these vague symptoms.[8] Hence, we might agree with Dr Ng in that psychostimulants may play a role in the treatment of patients with major depression, in particular for patients with profound such symptoms.

As Dr Ng stated, our patients may have had few or low levels of fatigue, apathy, hypersomnia, or psychomotor retardation-potential target symptoms of stimulant augmentation, which might have partly contributed to our study results. However, we do not have any evidence supporting this possibility because any validated rating scales specifically measuring fatigue or decreased energy were not applied in our study. In fact, the clear consensus about the definition, phenomenology, pathophysiology, and role of fatigue in major depression is still lacking and much more complicated in psychiatry because the understanding of fatigue is highly complex and multidimensional, considering difficulties discerning specific causes and overlapping symptom domain of fatigue with psychiatric disorders.[8] We agree that decreased energy and fatigue are common symptoms of major depression, but trying to quantify "fatigue or decreased energy" in depressed patients is a very challenging issue because common rating scales such as Hamilton Depression Rating Scale and Montgomery-Asberg Depression Rating Scale do not have a specific item exactly quantifying it to be validated in both clinical practice and research field.[8] That is, items in some depression rating scales may have very much similarities to the notion of fatigue, decreased energy, or retardation.[8] However, the imprecision has been existing until today, and accordingly, it should be left for future researches. Finally, our sample power (patients n = 30 vs placebo n = 30) and the patients' characteristics do not allow any subanalyses. It may possibly lead to false-positive findings due to statistical issues even if some intriguing results might have produced. Hence, we would only be able to exactly address Dr Ng's keen comments through randomized, double-blind, placebo-controlled trials with adequately powered and a priori hypothesis in the future.

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Rater Scoring Variability in the Serial Assessment of Anxiety Symptoms

To the Editors:

Scoring variability by raters in central nervous system clinical trials can adversely affect trial results by decreasing statistical power and increasing the possibility of type II error. Measurement sensitivity is particularly relevant in studies of generalized anxiety disorder (GAD) where the Hamilton Rating Scale for Anxiety (HAM-A) is often used as the primary efficacy measure, despite its limitations.[1,2] Generalized anxiety disorder studies using the HAM-A often reveal broad scoring variance, narrow drug- to-placebo differences, and a poor-to-moderate overall effect-size.[3–5] The broad scoring variability has been attributed, in part, to poor rating accuracy and the insensitivity of the rating instrument.[6–8]

One factor influencing rating accuracy is the large number of inexperienced raters participating in clinical trials. It has been reported that 15% of potential HAM-A raters have had no previous experience or training with this specific instrument when they arrive at investigator meetings and that formal rater training can significantly reduce interrater scoring variability.[8,9] The present study examined rater scoring variability and the ability of raters to detect clinical change during 4 sequential patient visits as measured by the HAM-A and Clinical Global Impression (CGI) instruments.[1,10]

Fifty-three clinicians currently employed as raters at clinical trial sites in the United States consented to participate in a "ratings project" for which they were compensated. All 53 raters had used the HAM-A and CGI before this study (mean use of the HAM-A, 5.5 ± 3.6 years). Forty-eight respondents (91%) had more than 3 years of clinical experience working with GAD patients. Hence, these raters had both previous exposure to the rating instruments and experience with GAD patients. Fourteen respondents (26%) were physicians, 6 (11%) were doctoral level psychologists, 12 (23%) were master's level clinicians, and 21 (40%) had bachelor's or associate level degrees.

The 53 raters were stratified into 2 groups based on a self-reported survey asking demographic information and questions about previous rater training experiences. The 36 raters who had attended at least 1 United BioSource Corporation (UBC)–PharmaStar training session for the HAM-A were categorized as Group A. The 17 raters who had not participated in a UBC training program specifically for the HAM-A scale were designated as Group B. Statistical analyses included analysis of variance, Levine test for equality of variance, and χ^2 tests.

The raters observed and scored DVD videos showing 4 sequential interviews of 2 anxious patients using the structured interview guide for the Hamilton Anxiety Scale as developed by Williams.[11] The interviews depicted 2 fictionalized patients (portrayed by actors) with moderate-severe anxiety symptoms at baseline followed by 3 additional visits similar to the schedule

of a typical GAD trial. The baseline interview for each patient was identified, but the visit sequence of the remaining 3 interviews was blinded to the rater and presented out of chronological sequence.

The HAM-A scores for Patient 1 revealed a gradual clinical improvement across the 4 interviews from a group mean (SD) of 24.5 (±2.8) at baseline to 16.72 (±1.8) at Visit 2, 14.32 (±1.8) at Visit 3, and 10.25 (±1.3) at end point (Visit 4). Alternatively, Patient 2 revealed some fluctuation but no substantial clinical change in serial HAM-A scores with a baseline group mean (SD) of 27.5 (±2.1) followed by 29.15 (±3.4), 23.15 (±2.3), and 25.8 (±2.3) at end point (Visit 4). Repeated-measures analysis of variance for the 8 interviews revealed a main effect for training group. Group A raters had significantly higher mean HAM-A scores than Group B raters: $F_{1,415} = 5.69$; $P < 0.02$.

Scoring variability between groups was examined for each of the 3 measures (HAM-A, CGI-S, and CGI-I) across the 8 interviews. Levine tests for equality of variance were performed comparing the 2 groups (Table 1). The trained Group A raters had significantly lower cumulative HAM-A scoring variance ($P = 0.013$) and significantly lower cumulative CGI-S scoring variance ($P < 0.0001$) than Group B raters. The CGI-I revealed a nonsignificant trend for lower variance in Group A than Group B raters ($P = 0.11$).

Serial assessments of the same subject enabled an analysis of each rater's ability to detect clinical change in the patient who improved (Patient 1). Using a criterion of 50% or greater improvement of HAM-A scores from baseline to end point as the measure of treatment response, 8 (15%) of the 53 raters failed to detect clinical improvement in Patient 1. Previous clinical experience or medical degree did not differentiate these 8 raters from the other 45 raters. However, only 3 of the 36

TABLE 1. Levine Tests of Equality of Variance

	Group A	Group B	*P*
HAM-A	2.05	2.38	0.013
CGI-S	0.52	0.67	<0.0001
CGI-I	0.51	0.56	0.113

Group A raters (8%) in contrast to 5 of the 17 Group B raters (29%) failed to detect clinical improvement in Patient 1 ($\chi^2_1 = 4.00$; $P < 0.05$).

Evaluation of individual raters' CGI-I scores revealed that all raters correctly rated Patient 1 as improved. Conversely, Patient 2 did not improve. However, CGI-I scores for Patient 2 revealed a nonsignificant trend such that only 4 Group A raters (11%) in contrast to 5 Group B raters (29%) incorrectly scored Patient 2 as mildly improved at end point ($\chi^2_1 = 2.74$; $P < 0.1$).

DISCUSSION

In this study, raters who reported that they had participated in at least 1 formal HAM-A training program with UBC (Group A) revealed significantly less within-group variability on the HAM-A ($P = 0.013$) and CGI-S ($P < 0.0001$) than raters who reported that they had not participated in HAM-A training with UBC (Group B). Furthermore, the Group A raters correctly detected clinical improvement in Patient 1 significantly more often than the Group B raters ($P < 0.05$).

These findings suggest that some formal rater training decreases rater scoring variability and can improve detection of clinical change. These findings must be interpreted cautiously, given the small sample size and inherent methodological limitations. We did not have a comprehensive record of previous training or clinical experience for each rater and chose an arbitrary stratification of the groups based on UBC training experience.

It is noteworthy that most raters in this study did detect clinical improvement in Patient 1 (85%) and the corresponding lack of improvement in Patient 2 (83%). Given this success rate, it is striking that 29% of the Group B raters failed to detect improvement in Patient 1, and 29% incorrectly scored Patient 2 as improved.

It is self-evident that the identification and exclusion of less capable raters would improve overall study results. Inexperienced raters are often unfamiliar with the administrative procedures and scoring conventions that seek to standardize the relatively subjective scoring instruments used in CNS trials. Clearly, more stringent standards for

rater eligibility and required training programs for "novice" raters are necessary. It must be emphasized that the ability to accurately rate a videotaped interview conducted by an expert is only part of the rating process in clinical trials. Beyond scoring accuracy, training programs must also teach and assess clinical skills (interviewing competency) via demonstration and interactive skills training.[8,9]

There are many experienced raters who are trained and retrained repeatedly for each new clinical study. When is retraining enough? The threshold between the "novice" rater and the well-trained experienced rater has not been delineated. Rater training programs must acknowledge this distinction and provide graduated programming that offers new learning regardless of the level of experience.

This study supports the use of evaluating rater competency using a sequential visit model to assess the ability to detect clinical change and scoring accuracy.

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Augmentation of Clozapine's Antiagressive Properties With Lamotrigine in a Patient With Chronic Disorganized Schizophrenia

To the Editors:

Aggressive behavior is a verbal or physical act directed against a person or object that can potentially cause physical or emotional harm. Aggression during schizophrenia seems to be particularly common, having been reported to be the third most frequent psychiatric disorder with violent behavior after substance abuse and bipolar disorder in psychiatric inpatient population.[1] The antiaggressive properties of clozapine have been described both in patients with psychotic disorders (eg, schizophrenia) and in those with nonpsychotic disorders (eg, impulse control disorders and borderline personality disorder), suggesting a specific antiaggressive effect distinct from its antipsychotic effects.[2] Clozapine seems to have effects against both autoaggression and heteroaggression including all aspects described by the specific scales such as Overt Aggression

TABLE 1. Effects of Lamotrigine 200 mg/d on the OAS Score

Baseline (wk)		40		
Treatment Duration of Lamotrigine 200 mg/d (wk)	4	8	12	16
OAS Total score	30	17	10	4

Scale (OAS) that includes verbal assault and assault against objects, others, and self. Antiaggressive properties of mood stabilizers such as valproate and lamotrigine have also been investigated in borderline personality disorder in 2 randomized, double-blind, controlled clinical trials. The combination of lamotrigine plus clozapine is theoretically attractive, based on the possibility of synergistic antipsychotic effects that might be possible because of their antagonistic effects on glutamate neurotransmission, a system thought to be dysregulated during schizophrenia.[3] We present here the first case report, to our knowledge, describing possible synergistic effects of lamotrigine and clozapine in reducing aggressive behavior.

This was a case of a 38-year-old male patient (N.N.) with chronic (20 years) disorganized-type schizophrenia who had been to 4 previous hospitalizations and who had previously been treated with first-generation antipsychotic haloperidol and second-generation antipsychotic risperidone at the maximum dosage of 10 mg/d. However, according to his family, aggressive and hostile outburst remained frequent and unchanged, and he was considered to be treatment-resistant when he presented to our clinic for the first time with total OAS score of 55. Risperidone was discontinued, and clozapine was titrated to 400 mg/d. Because the response was not satisfactory, the dose was further increased to 800 mg/d and maintained for 4 consecutive weeks. Overt Aggression Scale total score improvement of −15 points was observed. However, significant aggression, especially verbal, still remained (OAS total score, 40). Therefore, lamotrigine was added, and the dose was increased, according to the manufacturer's prescribing information, to 200 mg/d. After 16 weeks of lamotrigine 200 mg/d, total OAS score was 4 and manifested as mild personal insults and door slamming (Table 1).

We conclude that the combination of lamotrigine plus clozapine has the potential for significant and possibly

synergistic antiaggressive properties distinct from any antipsychotic effects. Further placebo-controlled studies are needed to confirm or negate our findings.

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Difficulties in the Medical Treatment of Prolactinoma in a Patient With Schizophrenia—A Case Report With a Review of the Literature

To the Editors:

The current treatment of schizophrenia consists of antipsychotic drugs that antagonize the dopaminergic system.[1] On the other hand, dopamine agonists are used in several diseases, such as prolactin-secreting pituitary tumors. Before this treatment option for prolactinomas became available, there was often recurrence of the disease and a poor medical outcome. Therefore, dopamine agonist medication is the first-line therapy in patients with prolactinoma.[2]

CASE REPORT

Our patient had been diagnosed with schizophrenia at the age of 14 but did not

receive any medical treatment at that point. Menarche occurred when she was 17 years, and she gave birth to 2 children being 24 and 26 years of age. Medical treatment of her schizophrenia had been started with diazepam and metofenazate after the birth of her first child. After her second pregnancy, medication was switched to oral haloperidol 1.5 mg to 3 mg TID, oral biperiden 4 mg TID combined with intramuscular fluphenazine decanoate 6.25 mg once a week. In addition, she started taking oral contraceptives for 5 years. At age 31 with discontinuation of the hormonal treatment, secondary amenorrhea occurred, and she was again treated with oral contraceptives for several years. During acute schizophrenic episodes, the medication with oral contraceptives was temporarily discontinued. Those acute exacerbations of schizophrenia in the 1970s and 1980s were treated with increased doses of oral haloperidol up to 30 mg TID, oral biperiden 4 mg TID, and intramuscular fluphenazine decanoate 6.25 mg once a week. In addition, electroconvulsive therapy had been applied several times between December 1985 and May 1988. She was finally released and psychiatrically stable on the following medication: intramuscular fluphenazine decanoate 50 mg every 3 weeks, oral clozapine 50 mg TID, oral haloperidol 9 mg TID, and oral lithium 450 mg b.i.d.

In 1989 she was referred to our endocrine unit at the age of 38 years. She presented as a woman of normal weight (body mass index, 21 kg/m^2) with galactorrhea and amenorrhea and an otherwise normal clinical status. Laboratory results showed high serum prolactin levels (>1000 ng/mL) and suppression of the gonadal axis (LH = 3.0 mIE/mL; FSH = 4.7 mIE/mL; subnormal estrogen and progesterone levels). Thyroid function tests were normal (TSH = 0.7 mE/L, T4 = 95 nmol/L). A computed tomography (CT) scan showed a homogenous isodens tumor of 16 × 19-mm size within the sella turcica moderately accumulating contrast medium. The optical chiasm was reached but not yet lifted by the macroadenoma. Surgical intervention had been suggested but had been rejected by the patient. Therefore, treatment was started with oral bromocriptine 1.25 mg daily, raised to 7.5 mg per day after 2 weeks. Serum prolactin levels remained above upper assay levels (>1000 ng/mL), and bromocriptine was increased to 18.75 mg daily over the next year. The patient was seen on a regular basis during follow-up visits in our outpatient clinic. Due to suppression of the gonadal axis, she received hormone replacement therapy for several years. During schizophrenic episodes, bromocriptine was discontinued until recovery of the patient and then slowly started again. Schizophrenic episodes were treated with continuation and increased doses of oral haloperidol and increased dosage of oral clozapine. In

TABLE 1. Reported Cases With Prolactinoma and Psychotic Disorders in Which the Psychiatric Diagnosis Preceded the Diagnosis of Prolactinoma by at Least 5 Years

Sex	Age, yr	Psychiatric Diagnosis	Size of Prolactinoma	Time, yr	Therapy	Outcome	Follow-up Time, mo	Reference
Male	40	Paranoid schizophrenia	Macro	10	Bromocriptine + thioridazine/diazepam	Partial tumor regression	13	9
Male	42	Paranoid schizophrenia	Macro	15	Debulking adenomectomy, then bromocriptine + diazepam/thioridazine	Stable residual tumor	36	10
Female	24	Schizophrenia	Micro	5	Bromocriptine + thioridazine, then transsphenoidal removal	No recurrence	5	6
Male	48	Bipolar disorder	Macro	19	Failed hypophysectomy, quinagolide + haloperidol	Partial tumor regression	18	8
Female	43	Psychoses	Macro	22	Pituitary adenomectomy	No recurrence	24	8
Male	35	Epilepsy and schizophrenia	Macro	?	Cabergoline + quitiapine	Tumor regression	8	11

Age indicates age at diagnosis of prolactinoma; time, onset psychiatric disorder to onset prolactinoma; outcome, outcome regarding prolactinoma treatment; follow-up time, follow-up time after diagnosis of prolactinoma.

addition, oral diazepam and perazindimalonat were added. The patient's husband had been taking care of the increased doses of oral haloperidol and the discontinuing and starting of bromocriptine during these episodes resulting in only 2 severe schizophrenic events requiring hospitalization.

After 4 years of treatment, the tumor showed necrotic features, and the sella appeared wider measuring 8 mm in diameter. Serum prolactin levels had been decreasing continuously and reached levels around 500 ng/mL. Regular follow-up CT scan and magnetic resonance imaging scans showed less necrotic tissue area and unchanged remaining adenoma tissue. Bromocriptine had been maintained at levels between 10 and 12.5 mg daily ever since, and serum prolactin levels are stabilized at levels of 130 ng/mL. The patient is in a good general condition.

DISCUSSION

Several studies showed an increase of serum prolactin up to levels of 100 ng/mL in patients treated with haloperidol or other psychotropic agents, and single cases with prolactin elevations up to 365 ng/mL have been reported.[3] Our patient presented with high prolactin levels (>1000 ng/mL) 24 years after having started on haloperidol. These high prolactin levels are very unlikely to be caused by any antipsychotic agent and were suspicious of a prolactinoma. The CT scan of the pituitary region confirmed the suspicion of a macroprolactinoma. Pituitary surgery was the first choice of treatment due to the diagnosis of schizophrenia. However, pituitary operation might cause postoperatively panhypopituitarism and diabetes insip-

idus. The management of hormone replacement therapy in psychiatric patients remains a challenge. In general, pituitary surgery should only be used if there is a probability to remove the entire tumor. Radiotherapy remains an option for inoperable tumors, which did not respond to pharmacological treatment. However, our patient refused an operation, and medical treatment was mandatory. Having schizophrenia and a prolactinoma, the need for a combined simultaneous treatment with dopamine agonists and antagonists was imminent. This confronted us with 2 problems: First, dopamine agonists are known to minimize hyperprolactinemic side effects of haloperidol.[4] However, case reports show that bromocriptine may cause worsening of the mental status when applied to patients with mental disorders caused by a dysfunction of the dopaminergic system.[5] Our concern was that dopamine agonist therapy would increase the frequency of schizophrenic episodes. Second, dopamine antagonist might enhance growth of microprolactinoma or macroprolactinoma, which was reported in previous cases.[6,7] Because neuroleptics have D2 dopamine receptor antagonistic effects, therapy during a longer period might result in a continuous disinhibition of the lactotrophs, which might lead to cell hyperplasia and possibly to pituitary adenoma. However, up to now, it is not possible to conclude that the incidence of prolactinomas is increased among patients with psychosis on long-term neuroleptic treatment. The neuroleptic drug clozapine

was suggested to have the lowest effect on growth of prolactinoma and may be the neuroleptic treatment of choice in patients with prolactinoma and psychotic disorders.[8] Table 1 presents an overview of reported cases with prolactinoma and preceding psychiatric diagnosis.

In our case, we were trying to balance the dosage of both divertic treatment regimens very carefully. Even though dopamine agonist and antagonist therapy seem to have an antagonizing effect toward one another, serum prolactin levels dropped to a stable mean of 130 ng/mL. We think that, currently, the optimal equilibrium of both pharmaceuticals has been reached.

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