Stimulant Treatment of Frontotemporal Dementia in 8 Patients

Sir: Clinicians are often reluctant to use psychomotor stimulants in patients with disinhibition from frontal lobe dysfunction because of the concern that these medications will worsen behaviors or result in psychosis.[1] We contrasted the effects of dextroamphetamine and quetiapine, an atypical antipsychotic often used to treat agitation in dementia patients with cognitive and behavioral symptoms, in 8 patients with behavioral-variant frontotemporal dementia (FTD) in a double-blind crossover trial. We were interested in testing a stimulant for several reasons: (1) there is autopsy, cerebrospinal fluid, and imaging evidence of dopaminergic deficiencies in FTD (reviewed in Huey et al.[2]); (2) there is a clinical association between FTD and basal ganglia dopaminergic dysfunction (i.e., parkinsonism)[3]; and (3) executive dysfunction associated with psychiatric illness (e.g., attention-deficit/hyperactivity disorder) can improve with dopamine augmentation.[4]

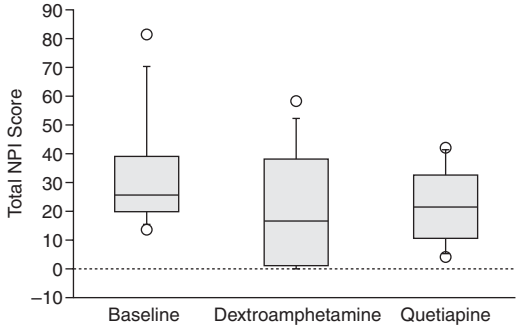
Method. All 8 patients had behavioral symptoms. Over 1 week, medication daily dosage was gradually increased to either 20 mg of dextroamphetamine or 150 mg of quetiapine in divided doses. The patients returned home on the target dose for 3 weeks before returning to our clinic for reevaluation. At this point, the patients were tapered to half the study medication for 2 days before discontinuation and then underwent washout for 1 week, and the process was then repeated with the other medication. Medication order was randomized, and the patients, caregivers, and clinicians were blinded to the order.

The individuals assigned durable power of attorney by the patients provided written consent, and all patients gave assent. The study was approved by an institutional review board and was conducted from November 2004 to August 2006. The primary measure of behavioral symptoms was the Neuropsychiatric Inventory (NPI),[5] and the primary cognitive measure was the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).[6]

Results. All patients were able to tolerate the full dose of dextroamphetamine. One patient experienced sedation on quetiapine treatment and was unable to tolerate the full dose. The most common adverse effect of both medications was sleep disturbance. The results for the total NPI can be seen in Figure 1. Using nonparametric methods (a 2-tailed Friedman test), there was a significant effect of treatment on the total NPI ($p = .05$). Post hoc Wilcoxon signed-rank tests showed that the total NPI was significantly lower than pretreatment baseline on dextroamphetamine ($p = .02$), but there was no significant difference between baseline and quetiapine, nor between quetiapine and dextroamphetamine. The NPI subscales that decreased the most on dextroamphetamine were apathy (2.8 points) and disinhibition (2.4 points). There was no significant overall effect of treatment on the RBANS.

The order of magnitude of this effect is large compared to that observed in pharmacologic trials for behavioral symptoms of Alzheimer's disease. A summary of available evidence concluded that the efficacy of atypical antipsychotics to treat behavioral symptoms in Alzheimer's disease is "small at best," with mean reductions in the total NPI score ranging from not significantly different from placebo to 8.8 points.[7] The sample size of this study was small, and thus these results should be viewed with caution.

Figure 1. Total Neuropsychiatric Inventory (NPI) Score at Baseline and After Dextroamphetamine and Quetiapine Treatment[a]



[a]Box encompasses the 25th and 75th percentiles. Horizontal line indicates the median, bars above and below the boxes indicate 10th and 90th percentiles, and points above and below the bars indicate range.

Contrary to conventional expectation, treatment with dextroamphetamine improved behavioral symptoms, including disinhibition, in patients with FTD. Medications that augment brain dopamine and norepinephrine, such as stimulants, are promising as a therapeutic strategy for the behavioral symptoms of FTD, which are particularly difficult for caregivers, care facilities, and clinicians to manage. However, given the small sample size and preliminary nature of this study, we do not at this time recommend stimulant treatment for the symptoms of FTD.

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Drs. Huey, Wassermann, and Grafman and Mr. Tierney all contributed to study design and execution, data analysis, and writing. Ms. Garcia worked on study design and execution. All authors have seen and approved the final version.

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Violent Parasomnia Associated With a Selective Serotonin Reuptake Inhibitor: A Case Report

Sir: We describe a case of parasomnia associated with the use of sertraline. Parasomnias are abnormal behavioral, autonomic nervous system, or experiential events that occur during the sleep period.[1,2] Various predisposing, priming, and precipitating factors can be involved with parasomnias; antidepressant medications have been associated with the emergence of sleepwalking.[3,4]

Case report. Mr. A, a 79-year-old white man without prior psychiatric hospitalization, experienced an episode of violent confusional behavior immediately following a morning awakening in August 2006.

Three months prior to the incident, his primary care physician, who had initiated sertraline therapy, referred him to a psychiatrist, who diagnosed DSM-IV posttraumatic stress disorder (PTSD) and major depressive disorder. Mr. A reported having 2 or 3 PTSD-related nightmares weekly since his return from World War II. He was on a ship that was attacked several times by Kamikazes. Later, he was on another ship that was near the Hiroshima and Nagasaki atomic bomb explosions at the end of the war. His wife reported that he was "always nervous" after he returned from his World War II military service. He was able to work despite having PTSD, but when he retired a few years previously, the symptoms worsened. He developed hypervigilance and was easily startled. He sought treatment when his nightmares worsened during the 2 months after Memorial Day and major depressive symptoms emerged, characterized by sadness, low energy, anhedonia, and fleeting suicidal thoughts.

Sertraline 25 mg/day as therapy for major depressive disorder and PTSD had been initiated a few weeks before the parasomnia episode. A week before the episode, the dose was increased to 50 mg daily, but Mr. A mistakenly increased it to 100 mg daily. He then noted marked, constant, coarse upper extremity tremor, which became so severe as to impede performance of simple tasks.

On the morning of the incident, he arose after being asleep for 5 or 6 hours, did not get dressed, and turned on the coffeepot. He then went outside to turn on a water pump, returned promptly to the house, and began stabbing at his wife with the handle of a knife. He was heard to say, "We have to end it all or we will go to jail." His movements were uncoordinated, and his wife was able to take the knife from him and escape to seek help from neighbors. She later reported that he did not "look himself" and said that "his expression was distant and blank." He later recalled feeling that "something bad had happened" and that he needed to get away. He dressed, picked up his cell phone, and proceeded to drive away in his automobile. After driving approximately 15 miles, he gained more consciousness and turned back to return home. He then received a phone call from the police and was arrested shortly thereafter and subsequently hospitalized at an inpatient psychiatric unit, where sertraline was discontinued. He then denied recollection of the event up to the time when he went into his car with a feeling of doom.

Mr. A's medical history includes herpes zoster, diabetes mellitus type II, and hypertension. There is no past history of any psychiatric treatment. He has no other history of parasomnia, including sleep talking. At the time of the event, he was taking allopurinol, felodipine, lovastatin, and omeprazole in addition to sertraline.

Physical examination results were unremarkable, with no tremor noted. Results of a mental status examination were likewise unremarkable, except for mild restlessness. He was alert and fully oriented, with intact sensorium. Neurologic consultation, performed on the third hospital day, revealed only a mild tremor in the first digit of his left hand. Computed tomography of the head showed "global loss of volume appropriate to his age," and magnetic resonance imaging showed scattered foci of increased T2 signal within the supraventricular and periventricular white matter, quite likely representing small vessel ischemic disease. There was no evidence of encephalitis.

Twelve days after the incident, the patient underwent overnight video-polysomnography including electromyographic monitoring of 4 limbs, and an expanded electroencephalographic seizure montage. The study was unremarkable apart from diminished sleep efficiency at 56%, some nonspecific spontaneous arousals from NREM and REM sleep, and snoring without clinically significant obstructive sleep apnea. His apnea-hypopnea index was 2.1, and his overall respiratory disturbance index was 5.7. One awakening from REM sleep was followed by extremity movement and vocalization, but normal chin muscle atonia during REM sleep was preserved. No complex behavior arising from NREM or REM sleep was recorded. Periodic leg movements occurred at a rate of 20 per hour during NREM sleep, unassociated with any sleep fragmentation. There was no clinical or electroencephalographic seizure activity.

Because Mr. A's unusual behavior had seemed to follow an apparently incomplete awakening from nocturnal sleep and was marked by complex but disorganized and remarkably uncharacteristic violence with amnesia, and no prior or subsequent indication of disturbed sensorium, it was thought that the event represented an atypical disorder of arousal manifesting as severe morning sleep inertia.[1,2] He was shocked to learn what he had done and was extremely remorseful. Ultimately, no criminal charges were filed.

Although the likelihood of a new-onset NREM parasomnia emerging spontaneously at age 79 years is very rare, this unusual and violent parasomnia event occurred in the context of (1) an inadvertently elevated dose of sertraline in a patient with major depressive disorder and PTSD; (2) A recent Memorial Day commemoration that was very stressful for this combat veteran with PTSD, and (3) relative sleep deprivation (the patient had slept

only 5 or 6 hours the night before). Differential diagnosis includes serotonin syndrome, nocturnal seizure disorder, REM or NREM sleep–related parasomnias (including extreme morning sleep inertia), obstructive sleep apnea, sleep related dissociative disorder (an extreme form of PTSD), and malingering. Serotonin syndrome–related delirium seemed to be ruled out by the absence of fever or elevated creatine phosphokinase. The patient had no history of seizure, nor were there any epileptiform findings on the polysomnogram. Selective serotonin reuptake inhibitor (SSRI) antidepressant use can precipitate REM sleep behavior disorder (RBD),[5] although in this case RBD was virtually excluded by his getting dressed, driving a car, and engaging in various other complex activities that required complex interaction with the environment with eyes open. RBD episodes usually occur with the eyes closed during dream-enactment when the person attends to the dream environment, rarely leaving the bedroom, and if so, by chance, such as going through an open doorway. Also, this patient did not remember most of the episode or any associated dreaming, unlike in RBD, in which patients have memory of the dreams they are enacting. Finally, there was no clinical suspicion or evidence suggesting the presence of sleep related dissociative disorder or malingering.

SSRIs appear to be associated with fragmentation of NREM sleep,[3,4] which can precipitate episodes of sleepwalking. Additionally, serotonin has been hypothesized as a link between disordered breathing and sleepwalking.[6] It is possible that increased serotonin activation can alter modulation of sleep/wake transition by dissociating the activity of serotonin neurons from the level of arousal, thus producing an incomplete awakening. This provides one hypothesis for medication-induced sleepwalking, which may be relevant to this case involving presumed subclinical sleep-disordered breathing (snoring), but does not explain occurrences of sleepwalking related to other psychotropic medications.

There are forensic implications for this case, with police being called to intervene on account of the patient's driving while in an impaired state, and also in view of the comment he made to his wife that "We have to end it all or we will go to jail" while he was stabbing at her (fortunately, in a confused fashion with the handle of a knife). His sleep-related violence (and associated verbalization) could otherwise have resulted in a fatal or life-threatening injury to his wife or himself, leading to a murder (or attempted murder) charge, or a death certificate reporting that the cause of his death was suicide. Sleep medicine forensic issues have been addressed for parasomnias with violence inadvertently directed toward others[1,3] and for the newly identified category of "parasomnia pseudo-suicide."[7]

Besides obtaining a careful history from the patient and spouse, conducting polysomnographic monitoring can provide important information, including diagnostic "rule-outs" in the setting of violent or injurious sleep-related behaviors. The role of psychotropic medications should be suspected in any newly emergent episodes of sleepwalking or other parasomnia associated with concurrent pharmacotherapy.

In conclusion, we believe that the most likely diagnosis in this case is SSRI-induced severe morning sleep inertia, a disorder of arousal with violent, confusional, and complex behaviors.

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

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A Polymorphism in the Angiotensin-Converting Enzyme Gene Is Associated With Smoking Behavior

Sir: Nicotine abuse and dependence is a complex addictive disorder with a pronounced genetic background.[1] In addition, it is one of the strongest risk factors for cardiovascular disorders (CVD). It has been extensively discussed whether the known high comorbidity between CVD and major depressive disorder (MDD) is more likely determined by biological, such as genetic, variables or by behavioral changes caused by depression, which in turn enhance cardiovascular risks. Functional polymorphisms of the angiotensin-converting enzyme (ACE) gene are susceptibility factors for MDD.[2,3] Furthermore, despite partly conflicting results, ACE gene variants have been linked to cardiovascular risk factors such as hypertension[4] and myocardial infarction.[5]

Here, we present data suggesting that variants of the 287-bp insertion (allele I)/deletion (allele D) polymorphism in intron 16 of the ACE gene represent a possible biological link between CVD and MDD via genetic modulation of smoking behavior in both depressed patients and healthy controls.

Method. The interdependency between genetic variables and smoking habits was investigated in a first sample of 483 physically healthy patients suffering from unipolar MDD (DSM-IV criteria). The study was approved by the local ethics committee of the Ludwig-Maximilian-University of Munich, and written informed consent was obtained from all subjects. Cardiovascular disorders as well as use of antihypertensive medication or statins were exclusion criteria. To confirm the results and to investigate a possible influence of the depressed state on smoking behavior, a second independent sample of 110 psychiatrically and cardiovascularly healthy controls was examined (Table 1). Patients and controls were recruited from August 2004 to

Table 1. Angiotensin-Converting Enzyme I/D Genotype, Demographics, Metabolic Risk Factors, and Smoking Behavior in MDD Patients and Controls[a]

Characteristic	Total	Angiotensin-Converting Enzyme I/D Genotype			χ^2 or F[b]	p[b]
		D/D	I/D	I/I		
MDD patients (sample 1)						
N	483	139	249	95		
Age, mean ± SEM, y	48.4 ± 0.7	50.2 ± 1.1	48.1 ± 1.0	46.3 ± 1.7	2.0	.13
Gender, male/female, %	37.1/62.9	41.2/58.8	34.4/65.6	31.9/68.1	1.9	.39
Smoking status, smoker/nonsmoker, %	11.0/89.0	16.5/83.5	9.6/90.4	6.3/93.7	**7.0**	**.03**
Daily cigarette consumption, mean ± SEM	5.6 ± 0.7	8.5 ± 1.5	4.5 ± 0.9	4.3 ± 2.0	**3.2**	**.044**
Metabolic risk factors, mean ± SEM						
BMI, kg/m^2	25.3 ± 0.23	25.7 ± 0.41	25.5 ± 0.35	24.3 ± 0.48	4.3	.12
Total cholesterol, mg/dL	225.6 ± 3.5	222.8 ± 6.6	223.5 ± 5.0	233.8 ± 8.9	1.62	.45
Triglycerides, mg/dL	140.3 ± 7.3	169.6 ± 17.8	124.0 ± 9.3	128.6 ± 11.3	5.2	.08
LDL, mg/dL	134.2 ± 5.8	132.6 ± 11.0	124.0 ± 6.5	165.0 ± 11.3	**6.8**	**.033**
HDL, mg/dL	57.7 ± 2.7	52.7 ± 5.3	58.9 ± 2.9	61.4 ± 7.3	3.3	.19
Fasting glucose, mg/dL	101.2 ± 2.1	101.7 ± 4.4	100.6 ± 2.9	101.1 ± 4.2	0.5	.78
Healthy controls (sample 2)						
N	110	29	57	24		
Age, mean ± SEM, y	54.3 ± 1.4	54.0 ± 2.5	53.0 ± 2.1	57.6 ± 2.6	0.9	.43
Gender, male/female, %	45.5/54.5	37.9/62.1	52.6/47.4	37.5/62.5	2.5	.29
Smoking status, smoker/nonsmoker, %	15.6/84.4	21.4/78.6	12.3/87.7	16.7/83.3	1.2	.54
Pack-years, mean ± SEM	6.6 ± 1.4	12.7 ± 4.3	4.9 ± 1.5	3.9 ± 1.6	**3.3**	**.040**

[a]After verification of the normal distribution of the investigated variables (Kolmogorov-Smirnov test), the univariate analysis of variance (ANOVA procedure, SPSS 15) confirmed that the actual cigarette consumption in major depressive disorder patients and the lifetime cigarette consumption measured in pack-years in a second confirmatory sample of cardiovascularly and psychiatrically healthy controls are highest in carriers of the ACE D/D genotype. Metabolic variables which were in part nonnormally distributed were analyzed using the nonparametric Kruskal-Wallis test.
[b]df = 2. Boldface indicates statistically significant values.
Abbreviations: BMI = body mass index, D = deletion allele, HDL = high-density lipoprotein, I = insertion allele, LDL = low-density lipoprotein, MDD = major depressive disorder, SEM = standard error of the mean.

December 2007. Due to recruitment of the control sample from an originally independent investigation, we obtained differential measures for actual daily and lifetime nicotine consumption.

Genotyping of the I/D polymorphism using PCR (polymerase chain reaction) amplification of the ACE I/D polymorphism was performed using the primers and methods described previously.[3] Statistical analyses included χ^2 tests for categorical variables and univariate analyses of variance (ANOVA procedure; SPSS for Windows, release 15.0.1; SPSS Inc., Chicago, Ill.) and, in the case of nonnormally distributed variables, nonparametric Kruskal-Wallis tests for continuous variables.

Results. In the first sample of 483 depressed patients, smoking habits were significantly related to ACE I/D genotypes: homozygosity for the D-allele enhanced the risk for being a smoker ($\chi^2 = 7$, $p = .03$). The number of daily smoked cigarettes was related to the ACE I/D genotype: homozygous carriers of the D-allele consumed about twice as many cigarettes in comparison to homozygous or heterozygous I-allele carriers. Demographic variables and metabolic risk factors showed no statistically significant differences with the exception of low-density lipoproteins.

In an independent sample of 110 cardiovascularly and psychiatrically healthy controls in which the lifetime consumption of nicotine was evaluated using the usual standardized measurement of pack-years (packs of 20 cigarettes per day × years of smoking), homozygous D-allele carriers also showed a significantly higher lifetime cigarette consumption ($F = 3.3$, $p = .04$) (Table 1).

This is the first report to our knowledge showing an association between the ACE gene I/D polymorphism and smoking behavior. Since the first studies suggesting an interdependency between genetics and tobacco consumption[6] were published, a variety of genetic associations with nicotine addiction and smoking behavior, e.g., the long allele of an insertion/deletion polymorphism in the promoter region of the serotonin transporter (5-HTTLPR),[7] have been reported. A genome-wide scan localized some genes associated with the risk of nicotine dependence in regions on chromosome 17, among others,[8] but effect sizes were only moderate, and there was a poor overlap with a second replication sample. Another genome-wide scan tried to identify loci for smoking rate in the Framingham Heart Study population and again found evidence for a linkage signal to chromosome 17,[9] which was even stronger if only European Americans were investigated.[10] A further genome-wide scan in a sample of twins could only replicate previous linkage findings for smoking phenotypes on 10q, 7q, and 11q, not on chromosome 17.[11]

In spite of these divergent results and even if nicotine dependence is a complex trait with both genetic and environmental influences, variants of the ACE gene, which are located in the cytogenetic region 17q23.3 on chromosome 17, may possibly therefore not only be responsible for the susceptibility to MDD[2,3] and enhance the risk for CVD,[4,5] but also contribute to an enhanced cardiovascular risk both in patients suffering from depression and in yet-healthy controls by promoting such a well-known risk factor as smoking.

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Corrections

In the article "Empirical Examination of a Proposed Refinement to DSM-IV Posttraumatic Stress Disorder Symptom Criteria Using the National Comorbidity Survey Replication Data" by Jon D. Elhai, Ph.D., and colleagues in the April 2008 issue (J Clin Psychiatry 2008;69:597–602), 2 inaccuracies were reported in the first paragraph of the Results section on page 599.

(1) The correct standard errors for lifetime diagnostic prevalence rates of PTSD are 0.360 for the original *DSM-IV* PTSD model and 0.351 for the Spitzer PTSD model.

(2) The binomial approximation z test that compared the *DSM-IV* and Spitzer lifetime PTSD prevalence rates was inaccurately reported as being statistically significant, because of an error the authors made in calculating this comparison. In fact, no statistically significant difference is found between these prevalence rates, $z = 1.17$, $p > .05$. Thus, the Spitzer model did not statistically change *DSM-IV* PTSD's prevalence rate.

In the article "The History and Current State of Antidepressant Clinical Trial Design: A Call to Action for Proof-of-Concept Studies" by Alan J. Gelenberg, M.D., and colleagues in the October 2008 issue (J Clin Psychiatry 2008;69:1513–1528), the following conference participants should have been acknowledged as follows:

In addition to the authors of this article, the following individuals participated in the conference "Advancing Signal Strength in Proof of Concept Studies in Major Depression," June 21–22, 2007: *Government and academia*: **Linda L. Carpenter, M.D.**, Butler Hospital/Brown University; **Ian A. Cook, M.D.**, Semel Institute for Neuroscience and Human Behavior at University of California, Los Angeles; **Wayne C. Drevets, M.D.**, National Institute of Mental Health; **Ronald S. Duman, Ph.D.**, Yale University School of Medicine; **Joel B. Greenhouse, Ph.D.**, Carnegie Mellon University; **John K. Hsiao, M.D.**, National Institute of Mental Health; **Anthony J. Rothschild, M.D.**, University of Massachusetts Medical School; **Holly A. Swartz, M.D.**, Western Psychiatric Institute and Clinic; **Howard Tennen, Ph.D.**, University of Connecticut Health Center; **Philip Sung-En Wang, M.D., Dr.P.H.**, National Institute of Mental Health; **Thomas P. Laughren, M.D.**, Food and Drug Administration. *Industry:* **Kathryn M. Connor, M.D., M.H.S.**, Merck Research Laboratories, Merck & Co., Inc.; **Aroon Datta, M.Sc.**, Forest Research Institute; **Judith Dunn, Ph.D.**, Sepracor; **Judith Jaeger, Ph.D.**, AstraZeneca; **Ronald Marcus, M.D.**, Bristol-Myers Squibb Company; **Randall L. Morrison, Ph.D.**, Ortho-McNeil Janssen Scientific Affairs, L.L.C., Johnson & Johnson; **Jorge A. Quiroz, M.D.**, Johnson & Johnson; **Tanya Ramey, M.D., Ph.D.**, Pfizer Inc.; **Brigitte A. Robertson, M.D.**, Sepracor; **Miqun Robinson, M.D., Ph.D.**, Sanofi-Aventis; **Sharon Rosenzweig-Lipson, Ph.D.**, Wyeth Research; **Mark A. Smith, M.D., Ph.D.**, AstraZeneca; **Gary Tong, M.D., Ph.D.**, Bristol-Myers Squibb Company.

The online versions of these articles have been corrected.