LETTERS TO THE EDITOR

High-Risk Groups for Charcoal-Burning Suicide Attempt in Hong Kong, China, 2004

Sir: In their letter "High-Risk Groups for Charcoal-Burning Suicide in Taiwan, 2001–2005," Lin and Lu[1] reported their finding that men aged 25 to 44 years who live in urban areas are the most likely individuals to use charcoal burning to die by suicide. The finding is consistent with our research, reported below, comparing the characteristics of people with suicide attempts by charcoal burning and by drug overdose in Hong Kong, China.

Method. Data on all people admitted to 2 hospitals of the New Territories East Cluster (Hong Kong, China) in 2004 because of charcoal-burning suicide attempt or drug overdose suicide attempt were collected from the records of a psychiatric consultation liaison team. Thirty-eight people with a charcoal-burning suicide attempt and 94 people with a drug overdose suicide attempt were identified for comparison. The consultation liaison services of the 2 hospitals were provided by the same team under the same consultant's supervision. The data were cross-checked by 2 investigators (E.L., C.-M.L.). Suicide attempts that included both charcoal burning and drug overdose were classified as charcoal-burning suicide attempts with concomitant use of other suicide methods. The reason for the suicide attempt was determined from the case record by the 2 investigators.

Results. The mean ± SD ages were 37 ± 10 years for the charcoal-burning group and 33 ± 10 years for the drug overdose group (p = .054). The male-to-female ratios were 1.2:1 for the charcoal-burning group and 1:3.9 for the drug overdose group (p < .001). Eighteen people (47%) in the charcoal-burning group and 2 people (2%) in the drug overdose group had concomitant use of other suicide methods (p < .001). Nine people (24%) in the charcoal-burning group and 5 people (5%) in the drug overdose group were living alone (p = .004). Financial stress was present in 11 people (29%) in the charcoal-burning group and 8 people (9%) in the drug overdose group (p = .001). There was no significant difference in marital status, employment, present psychiatric diagnosis, history of mental illness, or suicide history.

We found the characteristics of people with carbon monoxide poisoning suicide attempts by burning charcoal to be different from those of people with drug overdose suicide attempts. Being male and living alone with financial stress are risk factors for attempting suicide by burning charcoal rather than drug overdose.

As stated by Lin et al.,[2] estimation of the number of suicides by charcoal burning is not straightforward. Our study reviewed all people admitted to 2 hospitals in 2004 because of charcoal-burning suicide attempts and compared their sociodemographic characteristics with those of people who used other suicide attempt methods. Limitations included the relatively small sample size and lack of information about suicide deaths.

Through knowledge of the sociodemographic characteristics associated with charcoal-burning suicide attempts, suicide prevention strategy can be targeted to high-risk groups. A local cluster analysis study showed that people who died from charcoal-burning suicide exhibited more expressed suicide deliberation than those who used other suicide methods.[3] Apart from restricting access to charcoal and increasing general awareness of suicide-related behavior, increasing knowledge about complications of charcoal burning and accessibility of community support may be appropriate areas of focus for finding effective means to prevent these highly deliberate suicides.

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A Preliminary Study of fMRI-Guided rTMS in the Treatment of Generalized Anxiety Disorder: 6-Month Follow-Up

Sir: In our recent article,[1] we investigated the effects of functional magnetic resonance imaging (fMRI)-guided repetitive transcranial magnetic stimulation (rTMS) treatment for symptoms of generalized anxiety disorder (GAD). We found that low-frequency rTMS treatment, administered with frameless stereotaxy on the basis of individual functional imaging data, significantly decreased anxiety symptoms associated with GAD. However, when the article was published, the duration of the rTMS effects beyond the 3-week treatment period was not known. The possibility of long-lasting treatment effects, as has been observed with short-term electroconvulsive therapy,[2] could have significant clinical and economic implications for further utilization of rTMS for anxiety. We are writing this letter to report on the sustained improvement of our sample at 6-month follow-up.

Method. As previously reported in the original study, we recruited 10 participants aged 18 to 56 years with a DSM-IV diagnosis of GAD between August 2006 and March 2007. All eligible participants provided approved written consent prior to the initiation of any study-related procedure, and the study was approved by the institutional review board of University of California, Los Angeles.

All 10 participants completed 6 sessions of rTMS over the course of 3 weeks (2 treatments per week), and all 10 participants completed the 6-month follow-up phone interview. The targeted site of treatment was based on prefrontal activation, determined by fMRI using an anxiety-provoking gambling task. Stereotactically directed rTMS was applied using a Magstim Rapid Stimulator (Magstim, Spring Gardens, United Kingdom)

with a figure-of-8 coil (outer diameter 9 cm). Repetitive TMS was delivered at a frequency of 1 Hz for 15 minutes (900 total pulses). The intensity was set to 90% of the passive motor threshold for each participant.

Six months after their final rTMS treatment, we contacted participants by phone to obtain Hamilton Rating Scale for Anxiety (HAM-A)[3] and Patient Global Impression of Improvement (PGI-I)[4] scores. (Importantly, due to the fact that interviews occurred over the telephone, item 14 of the HAM-A could not be administered, as it requires clinician observation of the participant's behavior at the interview.) We also reviewed adverse events and concomitant treatments.

Results. The mean ± SD age of the original sample was 45.30 ± 12.1 years. Of the 10 individuals enrolled in the original study 5 (50%) were female and 5 (50%) were male. Three participants (30%) had been taking psychotropic medications (serotonin reuptake inhibitors) for at least 3 months prior to enrollment and continued throughout the original treatment period. At the 6-month follow-up, only 1 participant had continued taking psychotropic medication; the other 2 discontinued their regimens within 3 weeks of their final rTMS session. One participant began cognitive-behavioral therapy. No participants received additional rTMS or any other somatic treatment. Overall, 100% of individuals (n = 10) completed the 6-month follow-up phone interview.

In the original study, we found the mean HAM-A score decreased significantly from baseline (24.80 ± 7.37) to end of treatment (7.30 ± 8.02) (t = 6.044, p = .001). Six months after end of treatment, the mean HAM-A score (adjusted to exclude item 14) was 9.10 ± 2.77. One-way repeated-measures analysis of variance, with all scores adjusted to exclude item 14, indicated significant difference in means between baseline (22.50 ± 6.98), end of treatment (6.40 ± 7.17), and 6-month follow-up (9.10 ± 2.77) (F = 27.7, df = 2, p < .0001). Tukey honestly significant difference post hoc test indicated that adjusted scores were significantly different from baseline at end of treatment (p < .01) and at 6 months (p < .01), but the difference between scores at end of treatment and at 6 months was not significant (p > .05). The mean PGI-I rating at endpoint of the original study was 1 (very much improved since the initiation of treatment) and at 6 months was 2 (much improved since the initiation of treatment). Adverse events reported at 6-month follow-up were mild and included sweating, hot flashes, heart palpitations, and difficulty breathing.

Overall, the clinical status of the group remained improved since baseline, although it had minimally (but not statistically) worsened over the 6 months between assessments. Because the interviews occurred over the phone and without our direct observation, the Clinical Global Impressions-Severity of Illness and -Improvement scales and HAM-A item 14 were not performed. This limited our ability to classify responders and remitters according to the criteria used in our original study. Nevertheless, these data provide preliminary evidence that rTMS treatment may produce long-lasting benefits for symptoms of anxiety. Whether booster treatments may be necessary to maintain initial levels of improvement will need to be investigated in a rigorous research trial. The benefits of treatment and the reported adverse effects, which may have been physiological symptoms of GAD, will also need to be verified in future controlled studies with sham-treatment groups.

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Augmentation of Dopaminergic Agents for Major Depressive Disorder

Sir: We read with great interest the randomized, double-blind, placebo-controlled clinical trial (RCT) entitled "Osmotic-Release Oral System Methylphenidate Augmentation of Antidepressant Monotherapy in Major Depressive Disorder: Results of a Double-Blind, Randomized, Placebo-Controlled Trial" (osmotic-release oral system methylphenidate [OROS MPH] N = 73, placebo N = 72; mean dose of OROS MPH = 36.4 mg/day),[1] which followed our earlier 4-week RCT (OROS MPH N = 30, placebo N = 30; mean dose of OROS MPH = 34.2 mg/day).[2] In their article, Ravindran et al.[1] referenced our study only in the form of an abstract that was presented in a scientific meeting, without providing any detailed comparisons between the 2 studies. We therefore will briefly introduce our study results using a meta-analytic approach to extract findings from the 2 studies[1,2] in order to achieve better sample power. We also provide meta-analytic findings from 4 RCTs of modafinil augmentation for unipolar[3–5] and bipolar[6] depression.

When the results from the 2 RCTs[1,2] (OROS MPH N = 102; placebo N = 102) were merged, the standardized mean difference (SMD, calculated by Review Manager 5[7]) for mean changes in primary efficacy measures from baseline between OROS MPH and placebo was not significantly different (SMD = 0.15 [95% CI = –0.13 to 0.42], p = .3; heterogeneity, I^2 = 13%, p = .28), although the primary outcome measure was not the same between the 2 studies (Hamilton Rating Scale for Depression-21 item [HAM-D-21] score in Patkar et al.[2]; Montgomery-Asberg Depression Rating Scale in Ravindran et al.[1]). These trends were similar for secondary efficacy measures such as Clinical Global Impressions-Severity of Illness/Improvement scores. Hence, we may preliminarily assume that OROS MPH

augmentation of antidepressant therapy may not be efficacious in the treatment of depression on the basis of currently available data.

It is important to remember, however, that OROS MPH augmentation of antidepressant therapy has usually been tested in patients with ≥ 1 failed antidepressant trial, i.e., patients with partial response, recurrent depression, or treatment-resistant depression. Although the precise mechanism of the effect of dopamine in the pathogenesis of depression has not yet been fully explored, it is clear that dopamine is involved in the development and/or treatment of depression via action in several neuronal structures such as the nucleus accumbens and prefrontal cortex that are related to energy, fatigue, psychomotor function, and motivation and via intercommunication with various neurotransmitters such as serotonin and norepinephrine.[8]

Given their aforementioned short trial duration, inadequate dose titration, patient characteristics, and sample size, the 2 RCTs[1,2] of OROS MPH may not confirm the ineffectiveness of OROS augmentation of antidepressant therapy for treating depression. The question of whether OROS MPH may have substantial utility in the treatment of patients with a first episode of depression, bipolar depression, comorbid medical conditions, or predominant symptoms such as fatigue or loss of volition/cognition (spectrum of atypical features) may warrant subsequent clinical trials as well. Hence, we should postpone conclusions regarding the exact role of OROS MPH until attaining adequate findings from RCTs, particularly when we consider that depression has different symptomatic and clinical conditions.

Meanwhile, when we applied a meta-analytic approach to 4 RCTs of modafinil augmentation (modafinil N = 301, placebo N = 299) for patients with unipolar[3–5] and bipolar[6] depression, the SMD of the depression rating scales was significantly different for modafinil versus placebo (primary efficacy measures across the 4 RCTs: HAM-D-31 or -21 or Inventory of Depressive Symptomatology) (SMD = –0.45 [95% CI = –0.86 to 0.05], p = .03; heterogeneity, I^2 = 81%, p = .001). However, after exclusion of the bipolar RCT,[6] the significance disappeared (modafinil N = 260, placebo N = 255) (SMD = –0.33 [95% CI = –0.74 to 0.08], p = .12), indicating a possibly better efficacy of modafinil for bipolar depression than for unipolar depression. This may also indicate the potential role of other psychostimulants including OROS MPH in bipolar depression.

In conclusion, currently available findings from the 2 RCTs[1,2] about the role of OROS MPH augmentation failed to support a potential utility in the treatment of unipolar depression. However, more adequately powered RCTs with advanced designs, including potentially more responsive subpopulations, may prove its usefulness in clinical practice.

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Dr. Ravindran and Colleagues Reply

Sir: Thank you for offering us the opportunity to respond to the letter from Pae et al. that addresses our recent publication in the *Journal.*[1]

First, we would like to reiterate that the number of subjects was based on a power analysis, using the available data on expected change between groups and established a priori. While it is possible that if sample sizes were significantly increased the smaller differences might become statistically significant, this may not necessarily be of clinical significance or value.

Second, the merging of our data and those of Pae and colleagues' population may be questionable on both psychometric and statistical grounds because the 2 datasets used different primary efficacy measures, i.e., the Hamilton Rating Scale for Depression versus the Montgomery-Asberg Depression Rating Scale. Furthermore, their study had different entry and inclusion criteria, as well as a different duration of treatment.

Third, we would like to note that our manuscript was already in submission when their study was published. As such, we used their prior poster presentation[2] as the basis for discussion of their data. We feel that significant and appropriate prominence was

given to their data in both the introduction and discussion sections of our manuscript. We perused their letter carefully but failed to find any relevant information (in our opinion) that is not already noted in our publication.

Finally, while we agree with the need for and congratulate the authors on their "meta-analytic approach" to examining published literature on modafinil augmentation, we fail to understand the connection to our publication. The specific mode of action of modafinil is still unknown, but it is suggested to act on the hypothalamic wakefulness center and by the activation of histamine and orexin/hypocretin neurons.[3] While modafinil is also postulated to have some effect on dopaminergic and noradrenergic neurons, it differs from the classic stimulants such as methylphenidate and amphetamine in structure, neurochemical profile, and behavioral effects.[3,4]

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Correction

In the ACADEMIC HIGHLIGHTS section "A Roadmap to Key Pharmacologic Principles in Using Antipsychotics in the Treatment of Older Patients" in the January 2009 issue (J Clin Psychiatry 2009;70[1]:131–138), the year that the educational grant was given was omitted. The last sentence of the first paragraph (left column, page 131) should read: "Support for this project was provided by an educational grant from Bristol-Myers Squibb, Inc., awarded in November 2005."

The online version of this section has been corrected.