48 and 56. Retrospective chart review revealed that this participant has a history of weight instability and also experienced an alteration in her psychotic medication regimen that corresponded with the period of weight gain. It was noted that the other participant who gained weight (4 kg) had been participating in community reintegration activities outside the hospital during the period of weight gain, where the participant’s diet was not controlled.

**DISCUSSION**

The present findings offer encouragement that a modest contribution to weight management for patients on psychotropic polypharmacy regimens may be provided by metformin, irrespective of minimal participation in exercise programming. Furthermore, the data show that weight loss continued over a 40-week period. However, metformin’s effect on weight is modest and perhaps not sufficient to stave off the high risk of early mortality in this population. Indeed, it remains to be seen whether metformin’s effect can be sustained in the long term for SMI patients, especially in regard to delaying the onset of T2D and metabolic syndrome as has been demonstrated with healthy adults in the ADA’s Prevention of Diabetes Program.

Given our duty as health care providers to reduce the risk of our treatments (ie, psychiatric medications) to our patients, we are obligated to take an aggressive approach to weight management. Metformin therapy seems to be a good starting point. However, although group data from this performance improvement project demonstrate a positive effect of metformin on weight for almost 1 year, at the individual level, not all participants benefited from the intervention. Consequently, we would suggest that combined trials of metformin and other weight-modulating drugs be initiated (see Maayan et al for a review of the efficacy of various weight-reducing drugs), with the goal of increasing the range of medications available for those patients who do not respond to metformin therapy. Future work on the genetics of responsiveness to metformin may eventually allow for its more efficient use. Indeed, Zhang et al has provided evidence for the involvement of the leptin promoter in clozapine-associated weight gain, and Fernandez et al has provided evidence for the association of the leptin promoter in metformin response. Thus, future research on the pharmacogenomics of metformin may prove especially helpful for guiding metformin therapy.

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**Trauma Reactivation Under the Influence of Propranolol Decreases Posttraumatic Stress Symptoms and Disorder**

**To the Editors:**

The β-adrenergic receptor blocker propranolol, when administered shortly after the reactivation of conditioned fear and other memories, can reduce the strength of those memories through blockade of reconsolidation in animals. Propranolol also can reduce the strength of newly acquired emotional memories in healthy participants and in some—but not all—trauma-exposed clinical samples. Propranolol may also attenuate the emotional strength of long-standing traumatic memories in posttraumatic stress disorder (PTSD) and, therefore, represent a novel treatment approach. In a small randomized controlled trial, posttraumatic propranolol produced a decrease 1 week later in physiological responding during traumatic script-driven imagery. Propranolol also reduced PTSD symptoms, but the advantage over placebo, 19% versus 11%, was not significant. However, only 1 dose of treatment was provided in this proof-of-concept study. We wondered whether a greater number of treatment sessions would lead to a clinically meaningful improvement, and whether this improvement would be long lasting. We report on the results of 3 independent open-label trials designed to examine these questions.

**METHOD**

**Participants**

Participants were aged 18 to 65 years and met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text

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Revised, criteria for chronic PTSD. Exclusion criteria included a history of traumatic brain injury; a current or past psychotic, bipolar, or substance dependence disorder; a previous adverse reaction to a β-blocker; current use of a medication that could involve dangerous interactions with propranolol, including antidepressants that are cytochrome P450 2D6 inhibitors (antidepressants with no such interactions were not an exclusion criteria); a medical condition that contraindicated the administration of propranolol (e.g., asthma, heart problems, and diabetes); pregnancy or breast-feeding; or participation in any form of psychotherapy other than supportive. Participants gave written informed consent. All procedures were approved by the local ethics committee.

Study Design and Procedures

Study 1 involved 28 participants recruited via the newspaper in Montreal (Québec), Canada. These participants reported the following index traumatic events: motor vehicle accident (3), participation in a military UN peacekeeping mission (3), physical assault (5), assault with a weapon (2), sexual abuse (3), incest (5), severe physical abuse during childhood (3) or other (4). The study comprised a pretreatment assessment, 6 treatment sessions, a posttreatment assessment, and a 6-month follow-up. Participants were 96% whites and 68% women, with a mean age of 37.9 years (SD, 9.5), and a mean time elapsed since the traumatic event of 201.4 months (SD, 178.3; range, 3–540; median, 180). Comorbidity determined from a structured interview7 included major depressive disorder (8), social phobia (8) obsessive-compulsive disorder (6), generalized anxiety disorder (5), panic disorder with (2) and without (5) agoraphobia, agoraphobia without panic (2) bulimia (3) and anorexia nervosa (1).

Study 2 involved 7 participants recruited by word of mouth in Boston, Mass. These participants reported the following index traumatic events: motor vehicle accident (2), physical assault (1), assault with a weapon (1), rape (1), witness to family member’s fatal illness (1), and military combat (1). The study comprised a pretreatment assessment, 6 treatment sessions, a posttreatment assessment, and a 6-month follow-up. Participants were 100% white and 71% women, with a mean age of 40.1 years (SD, 11.8) and a mean time elapsed since the traumatic event of 120.0 months (SD, 118.0; range, 36–312; median, 132). Comorbidity included major depressive disorder (3) and panic disorder without agoraphobia (2).

Study 3 involved 32 participants taking part in an ongoing longitudinal study examining the long-term outcome of an industrial disaster that had occurred in Toulouse, France.10 Seven participants were treated with propranolol, and 25 refused treatment but agreed to serve as controls by taking part in 6-month postdisaster (performed previously), pretreatment, posttreatment, and 6-month follow-up assessments. The treated participants completed the assessments and 6 treatment sessions (as in studies 1 and 2). Treated participants were 71% women and 100% whites, with a mean age of 46.7 (SD, 18.3) years. The controls were 52% men and 100% whites, with a mean age of 47.9 (SD, 15.7) years. The 2 groups did not significantly differ on sex or age. The time elapsed since the traumatic event for all participants was 78 months. Comorbidity11 in the treated participants included MDD (3), social phobia (1), obsessive-compulsive disorder (1), generalized anxiety disorder (1), and agoraphobia without panic (2). Comorbidity data for the untreated controls are unavailable because of their more limited involvement.

PTSD Measures

The PTSD symptom score and diagnosis was determined by the Clinician-Administered PTSD Scale (CAPS) before and after treatment and at follow-up in studies 1 and 2. Intersession improvement was measured weekly in study 1 with the PTSD Checklist (PCL) before each treatment. In study 3, PTSD severity was measured by the PCL administered 6-months after disaster, before and after treatment, and at follow-up. In the treated group, PTSD was diagnosed with the Structured Clinical Interview for DSM-IV.11

Study Medication

Propranolol hydrochloride is a nonselective synthetic β1- and β2-adrenoceptor antagonist that crosses the blood brain barrier. Study 1 used a dose of 0.67 mg/kg short-acting (SA) oral propranolol in the first session. Ninety minutes later, an additional 1 mg/kg of long-acting (LA) oral propranolol was administered, providing that systolic blood pressure had not fallen by 10 mm Hg or more to lower than 100 mm Hg and that the SA dose was well tolerated, all of which were the case for every participant. In the subsequent sessions, the SA and LA doses were given simultaneously. The modal dose used was 40 mg SA and 60 mg LA, with means of 47.8 and 71.1 mg, respectively. Study 2 used the same protocol as study 1 but with fixed doses of 40 mg SA and 80 mg LA. Study 3 used 40 mg SA in the first session, followed 90 minutes later by 80 mg LA. In the subsequent sessions, only the 80 mg LA was administered. There were no serious adverse events and very few side effects, essentially limited to mild sedation.

Treatment Protocol

Ninety minutes after their first dose of propranolol, participants provided a written (studies 1 and 3) or oral (study 2) account of the index event that led to their current PTSD. During subsequent treatment sessions, 90 minutes after ingesting propranolol, they read aloud (or reenacted in study 2) their trauma account to the interviewer “as if they were back in the experience again.” Treatment sessions were purposefully kept short (<15–20 minutes) to minimize extinction.

Data Analysis

Study 1 data were analyzed using repeated-measures analysis of variance (ANOVA) with 9 measurement times (pretreatment, treatment sessions 1–6, posttreatment, and follow-up) and PCL score as the outcome measure. The data also were analyzed using a repeated-measures ANOVA, with 3 measurement times (pretreatment, posttreatment, and follow-up) and the CAPS score as the outcome measure. Study 2 data were analyzed using repeated-measures ANOVA with 3 measurement times (pretreatment, posttreatment, and follow-up), with the CAPS score as the outcome measure. Study 3 data were analyzed using a group (treated vs untreated) × time (6-month postdisaster, pretreatment, posttreatment, and follow-up) repeated-measures ANOVA and PCL score as the outcome measure. Degrees of freedom were Greenhouse-Geisser corrected. A 2-sided P value of less than 0.05 conferred statistical significance. Effect sizes were calculated as if the measures were independent, not paired, providing a more conservative estimate of treatment effect.

RESULTS

Study 1

As shown in Figure 1, mean (SD) PCL total scores at pretreatment, treatment sessions 1–6, posttreatment, and follow-up were as follows: 60.4 (11.4), 53.3 (11.6), 49.8 (13.5), 46.8 (13.2), 45.7 (14.0), 44.0 (13.1), 40.5 (15.8), 37.9 (14.9), and 36.0 (15.1), respectively. The decrease in PTSD scores across time was highly significant (F14,65, 100,40 = 22.31, P < 0.001). The pretreatment versus posttreatment contrast
was significant ($t_{27} = 8.81, P < 0.001$), as was the pretreatment versus follow-up contrast ($t_{27} = 8.22, P < 0.001$). These contrasts translated into very large effect sizes of Cohen $d = 1.70$ and $d = 1.82$. This corresponded to symptomatic improvements of 52% and 56%, respectively. Mean (SD) CAPS scores at pretreatment, posttreatment, and follow-up assessments were 71.8 (18.6), 45.8 (21.9), and 42.7 (24.6), respectively. The decrease in PTSD scores across time was highly significant ($F_{2, 54} = 38.05, P < 0.001$). On the CAPS, 20 (71%) of 28 participants no longer met the full criteria for PTSD at follow-up.

Study 2

Mean (SD) CAPS total scores at pretreatment, posttreatment, and follow-up were 68.4 (15.8), 35.6 (31.2), and 34.1 (33.2), respectively. The repeated-measures ANOVA revealed a significant time effect ($F_{2, 12} = 14.03, P < 0.01$). Pretreatment CAPS scores were significantly higher than posttreatment ($t_{6} = 3.96, P < 0.01$) and follow-up ($t_{6} = 3.79, P < 0.01$). These contrasts translated into large effect sizes of $d = 1.33$ and $d = 1.32$, respectively, and improvements of 48% and 50%, respectively. Furthermore, 5 (71%) of the 7 participants no longer met full criteria for PTSD at follow-up.

Study 3

Mean (SD) PCL scores at 6 months postdisaster, pretreatment, posttreatment, and follow-up for the treatment group were as follows: 60.9 (5.3), 60.7 (4.1), 41.0 (4.3), and 38.4 (3.6), respectively, and those for the control group were as follows: 59.7 (2.5), 61.7 (2.3), 58.7 (2.7), and 58.7 (2.8), respectively. There was a significant group × time interaction ($F_{1, 5} = 54.99, P < 0.001$). As expected, the groups did not differ significantly from each other at the 6 months postdisaster ($t_{30} = 0.21, P = 0.83$) and pretreatment ($t_{30} = 0.20, P = 0.84$) assessments but did differ at the posttreatment ($t_{30} = 3.16, P < 0.01$) and follow-up ($t_{30} = 3.57, P < 0.01$) assessments. The treatment effect sizes were $d = 1.77$ in the propranolol versus $d = 0.24$ in the control group at posttreatment, and Cohen $d$ at follow-up were as follows: $d = 2.19$ versus $d = 0.23$. Pretreatment to posttreatment PTSD symptom improvement in the propranolol group was 45% versus 7% in the controls. At follow-up, these improvements were 51% versus 7%. Six (86%) of the 7 treated participants no longer met the criteria for PTSD at follow-up, compared with 2 (8%) of the 25 untreated participants ($P < 0.001$; Fisher exact test).

**DISCUSSION**

In 3 independent studies, 6 brief trauma reactivation sessions under the influence of propranolol brought about large PTSD symptom improvements. Such results extend our previous placebo-controlled psychophysiological results in 2 important ways. First, recalling one's traumatic experience under the influence of propranolol received on 6 occasions, rather than just once, produced a much larger symptom reduction, thereby demonstrating more clearly the clinical potential of this novel approach. The effect sizes reported compare favorably to those produced by exposure-based psychotherapies, yet they were obtained using a different approach that involves fewer and shorter sessions and virtually no side effects. Second, the treatment effects were shown to persist over time.

The studies took place in 3 different countries with men and women, but a lack of participants of minority ethnicity limits the generalizability of the findings. In study 3, the control group improved minimally over the course of the 6 months. However, conclusions based on this comparison group are limited by factors such as their self-selection against treatment and unmeasured comorbidity.

One explanation for our results is that propranolol blocked the reconsolidation of the traumatic memory, which in turn led to symptom reduction. Although our study lacked the necessary controls to show that reconsolidation blockade was the active therapeutic mechanism, a recent experimental study supported reconsolidation blockade by propranolol as the mechanism underlying the observed reduction in conditioned fear. Another potential explanation for the present findings is that the intervention induced extinction. Although we cannot rule out such an explanation, extinction-based treatment sessions are typically prolonged and involve a greater number of sessions. In fact, brief exposures may exacerbate symptoms. Still, this possibility could be examined in future studies by using a placebo reaction condition. Until then, the conclusion that propranolol was necessary for symptom improvement must await results of a double-blind, randomized, placebo-controlled trial. The current data make a compelling case for launching a rigorous randomized clinical trial. Positive results would add to the growing literature targeting neuroplasticity as a novel treatment approach for mental disorders.

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REFERENCES


Sertindole-Associated Deep Venous Thrombosis

To the Editors:

It has been documented that venous thromboembolism risk has a 7-fold increase among users of conventional antipsychotic agents who were younger than 60 years and free of major risk factors.1 In clinical practice, conventional antipsychotics are sometimes changed to atypical antipsychotics because of their favorable side effects and efficiency on negative symptoms. Although clear evidence is lacking, possible thromboembolic effects of atypical antipsychotics are observed in case reports and clinical investigations.2–5 Sertindole, a newly marketed atypical antipsychotic, after phase 4 investigation in our country, is a nonseeding atypical antipsychotic agent with a high selectivity for dopaminergic neurons in the mesolimbic system and also with affinity for serotonin 5-HT2A and 5-HT2C, and α1-adrenoreceptors.6,7

We describe a case of venous thromboembolism during sertindole treatment in a woman diagnosed with schizophrenia.

CASE REPORT

Ms M. is a 37-year-old single woman, elementary school graduate, and unemployed. She has a 5-year history of schizophrenia and presented to the First University School of Medicine, Department of Psychiatry, with complaints of reference delusions, avulsion, aloxia, voices commenting on behaviors, suicidal ideation, and affective flattening. She was admitted to the inpatient clinic without any resistance to admission. She had been followed by our clinic for nearly 2 years and had been admitted 2 times. She had no history of substance abuse and other Axis I disorders. There was also no history of familial psychiatric disorder. She was otherwise in good general physical health and had no personal or familial history of venous thromboembolism or oral contraceptives, acetylsalicylic acid, or any antiocoagulant use such as heparin or rivaroxaban. Although the patient had a body mass index of 25 kg/m², neither her weight nor her level of physical activity had significantly changed with antipsychotic medication. She had no identified cardiovascular risk factors including smoking. She had taken antipsychotics including typical and atypical antipsychotics during her illness period including haloperidol, olanzapine, and amisulpride. She was off medication for nearly 4 months. She was hospitalized in our inpatient clinic with the complaints mentioned above. The last treatment was discontinued, and sertindole 4 mg/d was started and titrated to 16 mg/d within 9 days. Her level of motion continued in a normal pattern, and she was not bedridden. On day 11 of the hospitalization, she complained of right leg edema. Two days later, redness and pain appeared in her right leg when she was walking. We immediately consulted with the department of cardiovascular surgery. Disabled coagulation profile, with abnormal concentrations of C-reactive protein and fibrinogen,