condition as a treatment in one analysis (i.e., cognitive training) and as a control in another (i.e., neurofeedback) would be inconsistent.

Can the effects of medication be accounted for? Arns and Strehl (4) also raise the possibility that different patterns of medication use in the treatment group compared with the comparison groups may have had an impact on the effect size reported in the Steiner et al. study (5). This point is well taken. Two-thirds of the medicated patients in the neurofeedback and cognitive training conditions reduced their medication, but no patients in the control condition did so. This may have led to an underestimation of the effects of treatment on core ADHD symptoms. Our published protocol directly addressed this issue by including an additional analysis of trials with no or low levels of medication. However, too few such trials were in the neurofeedback domain for such an analysis.

What constitutes neurofeedback? Arns and Strehl (4) also felt that the Lansbergen et al. study (6) should have been excluded as it used a "nonstandard" neurofeedback approach. This is a similar criticism to that raised by Chronis-Tuscano et al. (1) with regard to child-focused interventions in the behavioral intervention analysis. In fact, the Lansbergen et al. study used mainly standard theta and beta frequencies for neurofeedback (theta suppression and enhancement of sensorimotor rhythm, a low beta somatosensory motor rhythm for all but one patient). This is recommended (7), and it is similar to the ranges used in other studies included in the meta-analysis. Some additional individualization (as also used in this study) is common and is claimed to improve outcomes (8). However, the rapid automatic threshold adaptation employed in the Lansbergen et al. trial was discussed as a possible limitation by the authors themselves (6). Still, many neurofeedback parameters including threshold adjustments have not been systematically studied and standardized, even though they may have the potential to contribute to training success or failure. Our study protocol did not introduce revised neurofeedback standards, but we consider it critical that future trials "implement adequately blinded designs that do not compromise the quality of the treatment" (2).

In summary, the proposals by Arns and Strehl (4) to use adaptive cognitive training as the control condition in the Steiner et al. study (5) and to exclude the Lansbergen et al. study (6) for its use of nonstandard elements in their neurofeedback approach would have given a more positive result, as they eliminate the trials with the smallest effect sizes. However, rather than "strictly adhering" to our protocol, this would have meant a serious breach of it.

Given the potential impact that our meta-analysis (2) could have on practice, it is vital that our work is held up to the highest level of scrutiny. We are grateful to the letter writers for raising these points so that we could again reflect on and review our decisions and interpretations. In each case raised, we are confident that we made the appropriate decisions during the development of the protocol and the interpretation of the results. However, it is essential that the results of the meta-analysis are interpreted in a circumscribed manner, in keeping with the highly specific question we addressed (i.e., in relation to core ADHD symptoms) and the limitations of the literature we were reviewing. We are certain that both sets of letter writers would echo our conclusion that "Properly powered, randomized controlled trials with blinded, ecologically valid outcome measures are urgently needed, especially in the psychological treatment domain."

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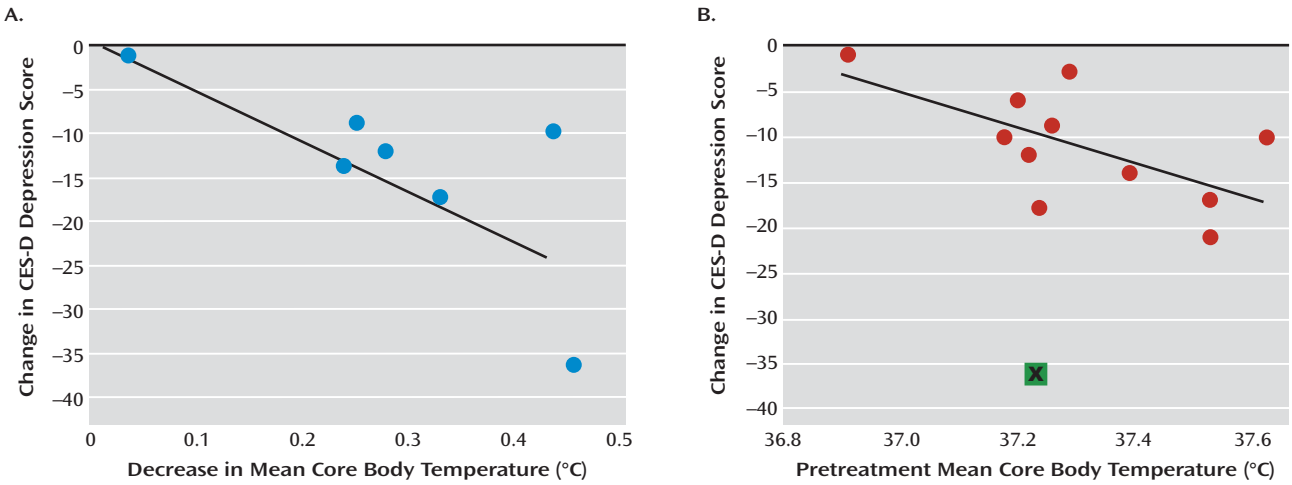
Whole-Body Hyperthermia for the Treatment of Major Depression: Associations With Thermoregulatory Cooling

TO THE EDITOR: Converging preclinical data suggest that stimulating a warm-sensitive thermoafferent spinoparabrachial pathway that projects from the skin (and other epithelial linings) to specific midbrain serotonergic nuclei produces antidepressant-like effects in animal models, while simultaneously inducing thermoregulatory cooling (1). Interestingly, several lines of evidence indicate that major depressive disorder may be characterized by suboptimal activity in this pathway, based on repeated observations that the disorder is associated with increased core body temperature, reduced

FIGURE 1. Associations Between 24-Hour Mean Core Body Temperature and Depressive Symptom Response to Whole-Body Hyperthermia[a]



[a] Panel A depicts the correlation between decreases in score on the Center for Epidemiologic Studies Depression Scale (CES-D) and decreases in 24-hour mean core body temperature from before treatment to 5 days after treatment with whole-body hyperthermia. Panel B depicts the correlation between 24-hour mean core body temperature before treatment and changes in CES-D depression scores from before treatment to 5 days after treatment, with one outlier removed (indicated by a green box with an "x" through it).

thermoregulatory cooling (e.g., sweating), and alterations in peripheral measures of serotonin (5-HT) activity, all of which are expected manifestations of impaired activity in the skin-to-brain-to-skin thermoregulatory circuit within which the ascending spinoparabrachial pathway and its CNS projections form core components (1).

We used ongoing clinical activities at a private alternative treatment hospital in Switzerland to evaluate the relevance of these observations for the treatment of depression by examining the acute antidepressant effects of mild whole-body hyperthermia in 16 medically healthy adults who were clinically diagnosed with major depressive disorder. Our interest in whole-body hyperthermia was based on animal data from our group demonstrating that exposure to warm temperature activates the spinoparabrachial pathway and the midbrain 5-HT nuclei to which it projects (1).

Mild-intensity whole-body hyperthermia was induced using a Heckel 2000 device, which uses water-cooled infrared lamps to heat the body (Heckel Medizintechnik GmbH, Esslingen, Germany). Using the Centers for Epidemiologic Studies Depression Scale (CES-D) (2), we found that a single session (mean session time, 126.7 minutes [SD=18.0]) induced a rapid, robust, and sustained reduction in depressive symptoms (CES-D score before treatment, mean=29.9 [SD=10.6]; 5 days after treatment, mean=19.2 [SD=12.3]; $t=4.53$, $df=15$, $p<0.001$, effect size=1.13). Thirteen of these patients received no other pharmacologic or psychotherapeutic intervention during the 5 days following whole-body hyperthermia, whereas three patients were being chronically treated with a selective serotonin reuptake inhibitor (SSRI), with no change in dosage during the study period. Interestingly, when examined separately, whole-body hyperthermia appeared to have no effect in the three individuals receiving SSRI treatment. With these three individuals removed from analysis, the effect size of the hyperthermia increased ($t=5.15$, $df=12$, $p<0.001$, effect size=1.4).

Mean core body temperature data were obtained in 12 patients before whole-body hyperthermia and in seven patients both before and 5 days after the intervention. Core temperature was assessed with either an indwelling temperature sensor (EndoTherm GmbH) inserted rectally in male patients or vaginally in female patients or by hourly measurement of rectal temperature while awake. The same method was used for both assessments in patients who had their core body temperature measured twice (i.e., before and 5 days after whole-body hyperthermia). The treatment induced significant and persistent thermoregulatory cooling, as reflected by a drop in mean core body temperature from 37.3°C (SD=0.24) before treatment to 37.0°C (SD=0.14) 5 days after treatment ($t=5.5$, $df=6$, $p=0.002$, effect size=2.1). Moreover, a trend-level large effect size correlation was observed between reductions in CES-D scores and reductions in mean core body temperatures in the same period ($r=0.73$, $df=4$, $p=0.06$) (Figure 1A). Finally, higher mean core body temperature prior to hyperthermia strongly correlated with degree of antidepressant response 5 days after treatment ($r=0.62$, $df=9$, $p=0.043$), with one statistical outlier removed (Figure 1B).

Taken together, these findings suggest that whole-body hyperthermia provides rapid and sustained relief of depressive symptoms and may do so by sensitizing physiological pathways important for thermoregulatory cooling that also affect brain regions implicated in the regulation of mood. Although this is the first study, to our knowledge, to examine this intervention specifically for major depressive disorder, our findings are consistent with reports that hyperthermia improves mood and quality of life when used in medically ill patients (3, 4).

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Suspected Dronabinol Withdrawal in an Elderly Cannabis-Naive Medically Ill Patient

To the Editor: Dronabinol is a synthetically produced oral delta-9-tetrahydrocannabinol (THC), the primary naturally occurring psychoactive constituent of cannabis. It is approved in the United States for the treatment of chemotherapy-induced nausea and vomiting and AIDS-associated anorexia and weight loss, but it has been used off-label for treatment of other conditions, including non-AIDS-related anorexia and weight loss (1). Like cannabis, dronabinol's tolerance, withdrawal, and psychoactive properties are mediated through the CB_1 receptor (1–4). Common symptoms of cannabinoid withdrawal include irritability, anxiety, decreased appetite or weight loss, restlessness, and sleep difficulties, including strange dreams. Less common symptoms include chills, depressed mood, stomach pain, shakiness, and sweating. The onset of withdrawal is within 24 hours of abstinence, peaks within 2–3 days, and lasts approximately 1–2 weeks. To date, withdrawal has only been described in animals and oral cannibinoid users in research studies. Here we describe the first case, to our knowledge, in a clinical setting.

Case Report

"Ms. A," a 71-year-old woman with a history of anxiety and postmyocardial infarction depression, was hospitalized for ischemic bowel and failure to thrive. Upon consultation, she was treated with duloxetine, methylphenidate, and supportive therapy, and her depressive symptoms gradually improved. Weeks later, she developed acute worsening of her mood, anxiety, sleep, appetite, nausea, and stomach pain, as well as visual hallucinations, tremors, and diaphoresis. Dronabinol, 10 mg b.i.d., which she had been taking for 3 months, and methylphenidate, 5 mg/day, had been abruptly stopped 3–4 days earlier for perceived ineffectiveness in improving appetite. Metoclopramide had also been discontinued because of its potential for tardive dyskinesia. Dronabinol withdrawal was suspected, and the drug was reinitiated at 5 mg b.i.d. along with quetiapine, 25 mg/day, for hallucinations and possible delirium. Over the next 2–6 days, all of the symptoms returned to recent baseline measurements, and the quetiapine was quickly tapered and discontinued without recurrence of symptoms.

Discussion

We attribute the onset and resolution of symptoms to the removal and addition of dronabinol because of their quick disappearance after reinitiation and their continued absence after discontinuing quetiapine. We recommend that potential withdrawal symptoms be considered during dronabinol use; tapering during discontinuation could prevent its occurrence. Additional studies are needed to better elucidate the details of phenomena such as the frequency of occurrence and dose-dependency in this population.

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