Human Investigations Committee approved the trial from which these data were extracted.

Results | We illustrate the value of this strategy, with a post hoc analysis of the effect of age, sex, and years of education on DUP, measured at a first-episode service in the 6 years prior to the launch of an ED campaign. To test our theory that growing awareness of the service would affect DUP over this period, the analysis was stratified by early (2006-2009) and late (2010-2012) epochs. Ordinary least-squares regression obtained a significant coefficient (SE) of −3.0 (1.3) (P = .02) on predicted mean DUP during the early vs late epoch (coefficient [SE], 0.1 [0.7]; P = .90). However, fit diagnostics implied severe violation of the normality assumption, invalidating this test. In contrast, QR revealed a significant differential effect of education by DUP quantile (**Figure**). Specifically, while no effect was found for the other demographic variables, more education was correlated with lower levels of extreme DUP during the early but not the late epoch (eg, coefficient [SE] at 90% percentile, −7.9 [3.0]; P = .01). As the service became better known to referral sources, the effect of greater educational attainment on improved access was likely muted. While this post hoc analysis can reveal only tentative inferences, it demonstrates the value of QR in interrogating actionable associations derived from clinical theory.

Discussion | Quantile regression analyses can inform messaging and outreach efforts for first-episode services that are contemplating ED efforts in their communities. A similar analysis, using ED as an independent variable, awaits results from an ongoing study[5] and will allow prospective assessment of the differential effect of this ED campaign across different subpopulations and across the full distribution of DUP.

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Published Online: August 31, 2016. doi:10.1001/jamapsychiatry.2016.2013.

Author Contributions: Dr Srihari had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Guloksuz, Li, Tek, Woods, McGlashan, Srihari.
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Study supervision: Tek, McGlashan, Srihari.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by grants R01MH103831 and RC1 MH088971 from the National Institutes of Health (Dr Srihari, principal investigator).

Role of the Funder/Sponsor: The National Institutes of Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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COMMENT & RESPONSE

Hyperthermia for Major Depressive Disorder?

To the Editor In their article in *JAMA Psychiatry*, Janssen and colleagues[1] describe an intriguing pilot study showing that whole-body hyperthermia was superior to sham in reducing depression. Their conjecture was that warm-sensitive afferent thermosensory pathways affect mood regulatory neural activity.[1] However, these data support an alternate hypothesis, which is that depression is associated with dysregulated mitochondrial function, the extent of which correlates with symptom severity and is associated with decreased oxidative energy generation and cerebral glucose use. Multiple psychiatric disorders are associated with a shift from aerobic to glycolytic energy generation. If it is shown that a therapy that increases mitochondrial energy generation also improves depressive symptoms, this would be useful, albeit indirect, proof of principle of this hypothesis.

Mitochondrial function is known to be influenced by many of the pathophysiological mechanisms currently implicated in depression including transmitters, such as dopamine, and pathways, such as inflammation. In contrast, at the opposite end of the mood spectrum, mania is associated with increased mitochondrial function. Many effective antidepressants and treatments, such as exercise, enhance mitochondrial function. Moreover, agents that acutely improve mood in humans and model mania in animals, such as amphetamines, have multiple effects that cumulatively serve to acutely enhance mitochondrial function. In the case of amphetamine, this acute increase in mitochondrial activity, if continued, is succeeded by longer-term degenerative effects as a result of the consequent oxidative stress. Germane to the hypothesis that mitochondria critically contribute to mood regulation, and directly relevant to the study by Janssen et al,[1] mitochondrial energy generation is temperature dependent; pyrexia is known to increase mitochondrial activity, while hypothermia decreases mitochondrial function.[2] In rats, mild heat stress increases indices of mitochondrial

metabolism (citrate synthase and cytochrome oxidase activity) and is associated with increased glucose uptake by muscle.[3] In muscle cells, a single exposure of 1-hour mild heat stress induces AMP-activated protein kinase and Sirt1 signaling and adaptive responses consistent with increased mitochondrial biogenesis and function including upregulated PGC-1α and a number of mitochondrial oxidative phosphorylation subunits.[4]

In summary, this study[1] provides unexpected proof of principle for the mitochondrial hypothesis of depression and raises many further avenues. It would be valuable to include indices of mitochondrial energy generation in future treatment studies. Additionally, mitochondrial function is potentially druggable, with many elements of mitochondrial metabolism amenable to intervention, and the first generation of such studies are currently under way.[5]

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Published Online: September 14, 2016. doi:10.1001/jamapsychiatry.2016.1532

Conflict of Interest Disclosures: Dr Berk is supported by a National Health and Medical Research Council Senior Principal Research Fellowship (1059660) and has received grant/research support from the National Institutes of Health, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, MBF, National Health and Medical Research Council, Beyond Blue, Rotary Health, Geelong Medical Research Foundation, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Meat and Livestock Board, Organon, Novartis, Mayne Pharma, Servier, and Woolworths; has been a speaker for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Lundbeck, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvay, and Wyeth; and served as a consultant to Allergan, AstraZeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Lundbeck, Merck, Pfizer, and Servier. No other disclosures were reported.

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To the Editor The study by Janssen et al[1] of a single exposure to whole-body hyperthermia relieving major depressive disorder is difficult to interpret and will need replication. The participants were highly selected from among long-time ill individuals with modest scores on the 17-item Hamilton Depression Rating Scale having less than 40% reduction with treatment. Which form of depression in the pool of "major depression" may be responsive to hyperthermia?

Melancholic depression, 1 of the 2 depression types that psychiatry recognized until the advent of *DSM-III* in 1980, is a more homogeneous biologically entity, defined by well-circumscribed clinical symptoms and a severity marker of abnormal cortisol metabolism, best studied by the dexamethasone suppression test.[2,3] If hyperthermia were to join the tricyclic antidepressants and electroconvulsive therapy on the list of antimelancholic agents, it would be a step forward. But electroconvulsive therapy continues to be plagued by stigma and the tricyclic antidepressants have significant adverse effects. Hyperthermia would open a new door.

Nonmelancholic depression, on the other hand—which used to be called *reactive depression*, *neurasthenia*, *psychoneurosis*, and *nerves*—is a very heterogeneous construct with little biological unity. Historically, it has been responsive to a variety of faddish agents, including ketamine infusions, transcranial magnetic stimulation, and UV light therapy. Joining this long list of remedies might be commercially profitable, but scarcely a step forward in the history of therapeutics.

Janssen and colleagues are to be congratulated for suggesting a new chapter in the treatment of depressive illness. The profession awaits replication, and hopefully these studies will focus on the better-defined major depression of melancholia.

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Published Online: September 14, 2016. doi:10.1001/jamapsychiatry.2016.1627.

Conflict of Interest Disclosures: None reported.

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In Reply We appreciate the insightful observations and questions raised by the letters from Fink and Shorter and Berk et al regarding our article.[1] Here, we respond to each letter in turn.

Fink and Shorter query whether whole-body hyperthermia (WBH) might have appreciable efficacy for major depressive disorder (MDD) with melancholic features. To enter our randomized trial of WBH, participants had to meet *DSM-IV-TR*–defined MDD and to have a 17-item Hamilton Depression Rating Scale score of 16or greater. Thus, we did not select for

individuals with melancholia as defined by the *DSM*. Here, we provide 2 somewhat conflicting observations.

First, although the Hamilton Depression Rating Scale does not specifically query for melancholia, it only allows for insomnia and loss of appetite/weight loss as neurovegetative symptoms and, in that way, biased our sample away from the symptoms of hyperphagia and/or hypersomnia, which are classic stigmata of the types of reactive depression to which Fink and Shorter refer.[2] The Hamilton Depression Rating Scale also queries psychomotor retardation and agitation, both of which are defining criteria of melancholic MDD. This would suggest that our sample might be more "melancholic" than reactive (or "atypical" in a more modern parlance), and that therefore WBH might indeed provide benefit for those with melancholia.

To examine this more rigorously, we extracted items from the Inventory of Depressive Symptoms–Self-Report that capture the 8 criteria of the melancholic specifier in *DSM-IV-TR* and examined whether WBH outperformed the sham control condition on just the sum of these 8 items across the 6-week study period. Although WBH outperformed sham on the sum of these items (maximally at week 4; adjusted mean difference, −3.67; 95% CI, −6.98 to −0.36; $P = .03$), the overall linear mixed model was nonsignificant ($F = 1.91$; $P = .18$), suggesting that WBH may be more effective for MDD generally than for melancholia specifically.

In regard to the letter by Berk et al, we could not agree more that mechanisms other than warm-sensitive afferent sensory pathways may be at play in the therapeutic effects we observed with WBH. In addition to the data cited by Berk et al regarding the ability of pyrexia to induce mitochondrial activity, we find the proposal that WBH might enhance mood via this mechanism to be especially interesting given the data from prior studies that hyperthermia produces acute immune system effects relevant to mitochondrial function,[3-5] although prior studies differed as to whether hyperthermia activates or quiets peripheral inflammatory activity. Data in preparation for publication by our group suggest that immune effects may indeed be relevant to the procedure's antidepressant potential. Future studies exploring the effect of WBH on mitochondrial activity—as well as mechanisms whereby WBH might affect this activity—are clearly indicated.

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Published Online: September 14, 2016. doi:10.1001/jamapsychiatry.2016.1917.

Conflict of Interest Disclosures: Dr Raison serves on the scientific advisory board of Usona Institute. No other disclosures were reported.

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Use of Clozapine in Schizophrenia

To the Editor Clozapine was not shown to be superior to other antipsychotic drugs in the comprehensive meta-analysis conducted by Samara et al.[1] This finding is in stark contrast to the landmark randomized clinical trial by Kane et al,[2] which has been backed by the cumulative wisdom of nearly 3 decades of clinical experience and observational evidence.

In clinical practice, clozapine is evidently underused,[3] and the conclusions of Samara et al[1] risk unjustifiably swaying more clinicians away from prescribing clozapine to people with schizophrenia who are far more unwell than those typically recruited in randomized clinical trials.

From an academic perspective, this clozapine "paradox" potentially challenges the current paradigm that positions meta-analysis at the top of medical evidence hierarchies,[4] reviving the view of Horwitz,[5] who advocated evaluating trials separately to avoid potentially misleading clinicians through assigning undue significance to amalgamating highly heterogeneous data.

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Published Online: July 20, 2016. doi:10.1001/jamapsychiatry.2016.0976.

Conflict of Interest Disclosures: Dr Mustafa has attended educational events sponsored by Eli Lilly, Janssen, Lundbeck, and Otsuka.

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To the Editor Does clozapine offer additional therapeutic benefit to patients who have received inadequate therapeutic benefit from other antipsychotic medications (APMs)? This is the question Samara et al[1] aimed to address in their article in *JAMA Psychiatry*.