Psychological Medicine

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Commentary

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Cite this article: Goldberg JF, Nasrallah HA (2022). Major depression is a serious and potentially fatal brain syndrome requiring pharmacotherapy or neuromodulation, and psychotherapy. *Psychological Medicine* **52**, 1423–1425. https://doi.org/10.1017/S0033291722001179

Received: 18 March 2022
Revised: 24 March 2022
Accepted: 5 April 2022
First published online: 3 May 2022

Keywords:
Antidepressants; electroconvulsive therapy; major depressive disorder; neuromodulation; pharmacotherapy

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Major depression is a serious and potentially fatal brain syndrome requiring pharmacotherapy or neuromodulation, and psychotherapy

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In their recent article, Read and Moncrieff (2022) beckon readers to turn back their intellectual clocks by nearly a century to revisit the anachronistic idea that clinical depression is driven mainly (if not solely) by social determinants, with little if any biological underpinning. Problematic with their thesis, from the outset, is their conflation of 'depression' or 'human suffering' in the everyday colloquial sense with the clinical syndrome of major depression that impairs mood, affect, attention, executive functioning, reward circuitry, hedonic capacity, feeding, sleep-wake cycle function, impulse control, and stimulus perception. Their neo-Szaszian view of depression fails to account for a large body of established observations and clinically relevant benchmarks from the last several decades. They also dismiss the entirety of medical efforts to achieve more effective biological therapies for disabling subtypes of depression.

First, regarding pathogenesis, one must acknowledge that not all victims of adversity develop major depressive disorder (MDD); biological diatheses predispose to (or protect against) individual-specific risk – analogous to the way not everyone exposed to ragweed develops hay fever, or not all smokers develop lung cancer. In MDD, genetic susceptibility loci (e.g. 5-HTTLPR or the Val66Met BDNF polymorphism) have been shown to moderate depression outcomes relative to adverse life events. Epigenetic regulation of gene expression in the setting of stress also confers resilience to depression by protecting against the passage of stress-induced pro-inflammatory cytokines across the vascular endothelium comprising the blood-brain barrier. And, lest one confuse modern nosology with the pre-DSM-III era, the presence of a major depressive episode (unlike an adjustment disorder with depressed mood) does not require or presume the existence of any environmental precipitant.

Studies of monozygotic twins reared apart further illustrate the importance of understanding the interplay of nature and nurture for translating biological predispositions to depression vis-à-vis environmental stresses. The seminal body of work by Kendler and colleagues, who at last count have accrued data on over 1.7 million twin pairs, shows an unambiguously increased probability of MDD occurring in monozygotic twins reared apart. Genome-wide association studies further demonstrate that novel susceptibility loci more than double the risk for developing depression when stratified by exposure to environmental adversity (Kendler et al., 1995).

From a structural-anatomic perspective, extensive postmortem and neuroimaging studies reveal lower overall brain volumes and reduced neuronal density in prefrontal cortical regions among MDD patients (reviewed by Anderson et al., 2020). Such findings have been accompanied by observations of downregulated gene expression associated with synaptic plasticity in major depression (Kang et al., 2012). Large-scale gene expression studies in postmortem brain tissue of MDD patients *v.* matched controls further identify an altered gene transcript 'molecular signature' of depression in structures such as the anterior cingulate-amygdala circuitry (Sibille et al., 2009).

Rather than construe the pathogenesis of clinical depression as an 'either/or' nature-*v.*-nurture proposition, modern formulations argue for interaction between individual biological predispositions (or genetics) and the environment (G × E) that is more complex or nuanced than simply chalking depression up to an expectable existential consequence of 'stress.' The interplay of neurobiology and psychosocial influences on mood is perhaps nowhere more evident than in findings from functional neuroimaging studies before and after cognitive behavioral therapy (CBT). Efficacious CBT for MDD produces changes in the metabolic activity of structures involved in emotional processing, such as cortico-limbic pathways (Goldapple et al., 2004), with normalization of resting state anterior cingulate-prefrontal connectivity on fMRI observable after successful CBT (Pantazatos et al., 2020). Similar changes in prefrontal network connectivity have been observed after successful treatment of MDD with selective serotonin reuptake inhibitors (Meyer et al., 2019). MDD is nowadays conceptualized as a disorder of neuroplasticity, with significant reductions in BDNF levels, decrement in neurogenesis, synaptic deficits, dendritic pathology and

hippocampal hypoplasia. Those neurobiological impairments are demonstrably countered not only by efficacious antidepressant psychotherapies, but by pharmacological antidepressants or neuromodulation modalities that confer neuroprotection [such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), or vagal nerve stimulation (VNS)].

Read and Moncrieff (2022) conflate the issue of whether antidepressants cause observable brain changes with questions about the robustness of their effects. We share their lamentation that the magnitude of effect could be greater for many available monoaminergic antidepressants. Overall effect sizes (ESs) of 0.30 place them roughly on par with ESs seen with statins for hypercholesterolemia or aspirin to prevent vascular disease (Leucht, Helfer, Gartlehner, & Davis, 2015). Meta-analyses of ECT for depression indicate large effect sizes as compared either to sham treatment (Cohen's d ~0.91) or pharmacotherapy (Cohen's d ~ 0.80) (UK ECT Review Group, 2003).

Part of the dilemma involving modest efficacy for many existing somatic therapies for MDD likely involves limitations of available technology – much as existing antineoplastics sometimes fail to produce remission for aggressive malignancies, but nevertheless can slow illness course and help somewhat to prolong survival. No less important to outcome in MDD is recognizing modifiable factors that influence prognosis and treatment response, such as delayed treatment initiation, subtherapeutic dosing/inadequate trials, nonadherence, and under-recognized/undertreated psychiatric or substance use comorbidity. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, where dismal response and remission rates were noted, most enrollees had highly recurrent or chronic depression and multiple psychiatric comorbidities – yielding less optimistic outcomes than might have occurred had earlier appropriate interventions been undertaken in a less complicated, less treatment-resistant cohort.

Finally, Read and Moncrieff (2022) again conflate two additional premises: the potential for somatic therapies to cause adverse effects with justification for eschewing them altogether. Somehow, framing a risk-benefit analysis in this manner fails to dissuade oncologists from offering toxic antineoplastic drugs to patients with hard-to-treat malignancies, or discourage health care providers from risking rib fractures and organ perforation from cardiopulmonary resuscitation (CPR) for out of hospital cardiac arrest, despite overall survival rates of only about 12%. All interventions (even placebos) carry risks, requiring risk-benefit analyses.

Remission remains an all-too-often elusive goal in mood disorders, but categorical response (i.e. improvement by > 50%) offers a pragmatic gauge for meaningful improvement relative to the balancing of risk. A recent Cochrane Review identified a median number-needed-to-treat (NNT) of 7 for selective serotonin reuptake inhibitors (SSRIs) and 9 for tricyclic antidepressants – comfortably within the parameter of <10 for a clinically meaningful effect as advocated by the National Institute for Clinical Excellence.

Risk-benefit analyses in medicine are quantifiable by the likelihood-to-be-helped-or-harmed (LHH) – i.e., the number-needed-to-harm (NNH; the higher, the better) divided by the NNT (the lower, the better); NNH / NNT ratios >>1 are favorable. Response rates for modern antidepressants yield NNT's ⩽10, with high NNHs (discontinuation due to adverse events), yielding LHHs uniformly >1 (Citrome, 2016). While greater strides remain to be achieved, there is no lack of evidence that current somatic therapies for major depression substantively reduce morbidity, as well as mortality from suicide (Lagerberg et al., 2021).

We are concerned that readers will perceive Read and Moncrieff's (2022) disparaging, antiscientifically skewed presentation – sourced partly from opinions and anecdotes posted on unmoderated internet chat sites – as reflecting clinical reality when that is simply not the case. Most clinicians who actually treat patients with severe depression would likely prefer having biological tools in their armamentarium, imperfect as they may be, to combat the serious and potentially fatal brain syndrome that is major depression.

Financial support. None.

Conflicts of interest. Joseph F. Goldberg, M.D. has been a consultant for BioXcel, Jazz Pharmaceuticals, Otsuka, Sage Pharmaceuticals, Sunovion, Supernus. He has served on the speakers bureau for Abbvie, Alkermes, Intracellular Therapies and Sunovion. He has received royalties from American Psychiatric Publishing, Inc., and Cambridge University Press.

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