Clinical Commentary

Biological Psychiatry

The Electrochemical Brain: Lessons From *The Bell Jar* and Interventional Psychiatry

Joseph J. Taylor, Hedy Kober, and David A. Ross

…because wherever I sat—on the deck of a ship or at a street café in Paris or Bangkok—I would be sitting under the same glass bell jar, stewing in my own sour air.

—Sylvia Plath, *The Bell Jar*

The Bell Jar, a haunting first-person narrative about depression and suicide, debuted in January 1963 under the pseudonym Victoria Lucas (1). Sylvia Plath told confidants that she disguised her identity because she questioned the literary value of the novel. One month later, Plath died by suicide via carbon monoxide poisoning; she was found in a carefully sealed kitchen with her head in an oven. Plath's suicide suggests that *The Bell Jar* is actually a *roman à clef*, or nonfiction with a veneer of fiction.

The novel opens on a sweltering summer day in 1953. Esther Greenwood, a witty college student from a Boston suburb, has begun a highly coveted internship at *Ladies Day* magazine in New York City. Unfortunately, the aspiring author is not herself; an insidious depression is slowly spoiling her experience and her normally vivid worldview. As the summer continues, Esther struggles to conceal morose moods and cognitive distortions. When the internship ends, she returns home to focus on writing but succumbs to mounting hopelessness and perceptual disturbances. After two brief psychiatric evaluations, Esther is prescribed an antiquated, anesthesia-free version of electroconvulsive therapy (ECT). It only takes one traumatic "treatment" for Esther to drop out of care. After several suicidal gestures, she pens a suicide note and attempts to overdose on sleeping pills. Esther survives the attempt and ultimately remits following a modernized version of ECT during a subsequent hospitalization.

Esther's treatment course mirrors that of Plath's and highlights the limitations of psychiatry at the time. Acutely ill patients had few treatment options, and psychiatry had yet to define itself as an evidence-based medical specialty. Four years earlier, the neurologist who developed the lobotomy had won a Nobel Prize in Physiology or Medicine. Some psychiatrists were still using this form of psychosurgery as a treatment for troubled descendants of "schizophrenogenic mothers." Indeed, many of the available interventions were used to control patients rather than treat them. ECT initially fit this description until it was improved, validated, and ethically practiced.

The central tenet of ECT is that electricity can be used to alter neurotransmission for therapeutic purposes. Shockingly, this idea dates to ancient civilizations that used electric rays and eels as medical devices. In the mid-18th century, capacitors replaced bioelectric sea creatures as brain stimulation tools. With this new tool, researchers attempted to reanimate decapitated livestock and cadavers to understand how the brain moves the body. These macabre methods spurred decades of neurophysiology research that ultimately established foundational brain–behavior relationships and revealed how neurons wire into synapses and networks. By the early 20th century, psychiatry was deeply invested in "the electric brain." Even Sigmund Freud conducted electrophysiological research as a young neurologist and then wrote extensively about human behavior as a means of discharging energy to maintain psychodynamic equilibrium.

Then everything changed. The rapid and unexpected discovery of chlorpromazine shook psychiatry, releasing seismic waves through Europe right around the time that Esther received her first course of ECT. Medications suddenly became treatments rather than sedatives. Shortly thereafter, the serendipitous discovery of the antidepressant effects of monoamine oxidase inhibitors and tricyclics further reinforced the notion that medications were the future of psychiatry. These early successes contributed to the reconceptualization of psychiatric illness in terms of disordered neurotransmitter systems. Selective serotonin reuptake inhibitors emerged during the peak of this phenomenon. By the late 20th century, psychiatry was deeply invested in "the chemical brain."

In a 21st century remake of *The Bell Jar*, Esther would probably have a cartoon understanding of the monoamine hypothesis of depression long before she meets a psychiatrist. Data suggest that direct-to-consumer "telepharmevangelism" (2) increases medication requests from patients, which in turn increases prescription rates and drug company profits (3). Esther might request an "antidepressant," an on- or off-label medication from one of several classes that targets one or many neurotransmitter systems. Her clinician would be likely to oblige, thus starting a trial-and-error medication odyssey.

Unfortunately, remakes are rarely as compelling as originals, and the thought of *The Bell Jar 2018* is particularly unappealing because it would spotlight the limitations of modern psychiatry. Antidepressants remain the most frequently prescribed class of psychiatric medications (4), despite offering relatively modest response and remission rates, as well as inconsistent effect sizes when compared with placebo (5). If the first drug fails, the second and third drugs are also likely to fail. Indeed, study after study has shown that only a fraction of patients with depression remit with medications. Prescription rates remain high, and more than 80% of those who take psychiatric medications report long-term use, yet depression remains the leading cause of disability worldwide.

Even though current psychiatric medications are inadequate for most patients, novel medications remain rare. For a host of

https://doi.org/10.1016/j.biopsych.2018.06.002
ISSN: 0006-3223

reasons, pharmaceutical companies have reduced or abandoned psychiatric drug development. Most "new" medications are only new in name, not in class or mechanism. Ultimately, it may be that neurotransmitter models are intrinsically flawed, and that chemical reductionism cannot capture the complexity of psychiatric disorders.

One way forward may be to look backward. What often gets lost in this chemical era is the basic principle that neurotransmission also requires electrical signals. Medications do not always work, but when they do it is because they ultimately modulate both the electrical and the chemical properties of the brain. Interventional psychiatry (IP) is an emerging branch of medicine that embraces this electrochemical dualism. The term "interventional" has been used in cardiology and other medical disciplines to describe procedures along the spectrum between standard care and surgery. Using a similar conceptual framework, the nascent field of IP features an array of electrical, electromagnetic, and chemical interventions for patients whose symptoms are refractory to standard care. These treatments are often used to augment psychotherapies and medications and are thought to alter both electrical and chemical aspects of neurotransmission. IP treatments have their own set of side effects, risks, and efficacy limitations, but they offer evidence-based hope for patients who fail to remit with routine treatments.

The goal of IP is to use brain stimulation techniques or acutely acting drug infusions to modulate the neural systems thought to be associated with refractory psychiatric symptoms (6). Data suggest that patients who fail two or three medications for depression are more likely to benefit from IP treatments than they are from serial on- and off-label medication trials that are highly unlikely to work. Two of the most common IP treatments are transcranial magnetic stimulation (TMS) and ECT. In TMS, a staccato magnetic field induces electricity in neurons, causing changes in neurotransmission and promoting plasticity in targeted circuits. In ECT, a therapeutic seizure leads to a large release of neurotransmitters and a rapid induction of neurogenesis. TMS is less efficacious than ECT but causes fewer side effects and is performed without anesthesia. Severely ill patients are most likely to benefit from ECT, a treatment that remains deeply stigmatized and underused despite being one of the most efficacious treatments in all of medicine (7). If these interventions fail, patients might be evaluated for experimental treatments such as ketamine, vagus nerve stimulation, and others.

One of the most exciting aspects of IP is that its electrochemical treatments can also be used as powerful research tools. Aside from their therapeutic effects, brain stimulation techniques are also useful for investigating clinical symptoms and neural systems. For example, researchers have paired TMS with electrophysiological and neuroimaging techniques in order to make causal inferences about cognitive processes and the neural systems and networks that instantiate them (8). Such studies have already provided insights into depression biotypes as well as the tantalizing possibility of optimizing treatment selection with biomarkers or predictive algorithms (9).

The field of psychiatry has come a long way since *The Bell Jar*, but Plath's life and fictionalized autobiography remain stark testimonies to the inadequacy of psychiatric models and treatments. Looking back, ECT may have saved Plath's life had it been used to augment the medication prescribed during her relapse (10). Looking forward, psychiatric models and treatments should be guided by both the electrical and the chemical properties of neurotransmission. Rooting psychiatry in neuroscience will ensure that more patient stories mirror the end of Plath's novel rather than her life: with cathartic remission. As Plath wrote, "All the heat and fear had purged itself. I felt surprisingly at peace. The bell jar hung suspended a few feet above my head. I was open to the circulating air."

Acknowledgments and Disclosures

Clinical Commentaries are produced in collaboration with the National Neuroscience Curriculum Initiative (NNCI). David Ross, in his dual roles as co-chair of the NNCI and Education Editor of *Biological Psychiatry*, manages the development of these commentaries but plays no role in the decision to publish each commentary. The NNCI is supported by the National Institutes of Health Grant Nos. R25 MH10107602S1 and R25 MH08646607S1.

This work was supported by National Institutes of Health Grant Nos. R25 MH071584 and T32 MH19961 (to JJT) and R01DA042911, R01DA043690, R56DA040699, P50DA09241, and R01MH102854 (to HK) as well as the Thomas P. Detre Fellowship Award in Translational Neuroscience Research (to JJT) and the Oscar M. Ruebhausen Fund (to HK).

The authors report no biomedical financial interests or potential conflicts of interest.

Article Information

From the Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut.

Address correspondence to Joseph J. Taylor, M.D., Ph.D., Yale University School of Medicine, Department of Psychiatry, 300 George Street, Suite 901, New Haven, CT 06511; E-mail: joseph.taylor@yale.edu.

Received Jun 4, 2018; accepted Jun 7, 2018.

References

1. Plath S (2005): The Bell Jar. New York: Harper Perennial Modern Classics.
2. Peterson J, Baechle C, Thiele J, Dappen M, Fink TE (2004): Symptom Finger. Omaha, NE: Saddle Creek.
3. Becker SJ, Midoun MM (2016): Effects of direct-to-consumer advertising on patient prescription requests and physician prescribing: A systematic review of psychiatry-relevant studies. J Clin Psychiatry 77:e1293–e1300.
4. Moore TJ, Mattison DR (2017): Adult utilization of psychiatric drugs and differences by sex, age, and race. JAMA Intern Med 177:274–275.
5. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, *et al.* (2018): Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. Lancet 391:1357–1366.
6. Williams NR, Taylor JJ, Snipes JM, Short EB, Kantor EM, George MS (2014): Interventional psychiatry: How should psychiatric educators incorporate neuromodulation into training? Acad Psychiatry 38:168–176.
7. Sackeim HA (2017): Modern electroconvulsive therapy: Vastly improved yet greatly underused. JAMA Psychiatry 74:779–780.
8. Etkin A (2017): Addressing the causality gap in human psychiatric neuroscience. JAMA Psychiatry 75:3–4.
9. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, *et al.* (2017): Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med 23:28–38.
10. Bergsholm P (2017): Sylvia Plath recovered completely by electroconvulsive therapy at the age of 21 years and might have been saved by another series 9 years later. J ECT 33:e26.