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Recent Developments in the Treatment of Depression

Steven D. Hollon
Vanderbilt University

Zachary D. Cohen
University of Pennsylvania

Daisy R. Singla
University of Toronto, Sinai Health System

Paul W. Andrews
McMaster University

The cognitive and behavioral interventions can be as efficacious as antidepressant medications and more enduring, but some patients will be more likely to respond to one than the other. Recent work has focused on developing sophisticated selection algorithms using machine-learning approaches that answer the question, "What works best for whom?" Moreover, the vast majority of people suffering from depression reside in low- and middle-income countries where access to either psychotherapy or medications is virtually nonexistent. Great strides have been made in training nonspecialist providers (known as task sharing) to overcome this gap. Finally, recent work growing out of evolutionary psychology suggests that antidepressant medications may suppress symptoms at the expense of prolonging the underlying episode so as to increase the risk of relapse whenever someone tries to stop. We address each of these developments and their cumulative implications.

Keywords: cognitive behavior therapy; antidepressant medications; treatment selection algorithms, global mental health; iatrogenic effect

Daisy R. Singla is a Distinguished Fellow at the Medical Psychiatry Alliance and supported by an Academic Scholars Award by the Department of Psychiatry at the University of Toronto.

Address correspondence to Steven D. Hollon, Ph.D., Department of Psychology, 306 Wilson Hall, Nashville, TN, 37240; e-mail: steven.d.hollon@vanderbilt.edu.

Depression is one of the most prevalent of the psychiatric disorders and the leading cause of disability worldwide (Ferrari et al., 2013). Both antidepressant medication (ADM) and cognitive behavior therapy (CBT) have been shown to be efficacious in its treatment as has interpersonal psychotherapy (IPT), but response rates to any given treatment rarely rise above 50% (National Health Service, 2016). The situation is compounded in low- and middle-income countries (LMICs) where up to 95% of the population does not have access to minimally adequate treatments, compared to 20% in high-income countries (HICs; Thornicroft et al., 2017).

In this article, we describe recent efforts to use machine learning to generate treatment selection algorithms that can be used to identify the optimal treatment for a given patient (Cohen & DeRubeis, 2018). To the extent that different people respond to different interventions, it may be possible to boost overall response rates by giving each patient whatever treatment works best for him or her. Our ability to do that has grown exponentially in the last half decade and we now have the capacity to address the question first raised half a century ago: "What treatment, by whom, is most effective for this individual with that specific problem, and under which set of circumstances" (Paul, 1967). This is the essence of *precision medicine*.

Similar strides have been made to close the treatment gap in global mental health. This is being

done primarily through the training of nonspecialist providers (NSPs)—individuals with no formal training in mental health care (van Ginneken et al., 2013)—in a parsimonious set of common and specific elements that address cognitive, behavioral, emotional, and interpersonal elements (Singla et al., 2017). This process, referred to as task sharing, has been shown to be effective, thus making efficacious interventions potentially accessible to large segments of the population who have never had access before. Another important adaptation is providing treatment where it is most convenient for the patient (Singla, Raviola, & Patel, 2018). These are two of the key features of *global mental health*.

Finally, the selective serotonin reuptake inhibitors (SSRIs) are the second most widely prescribed medications in the world (after statins), but may be neither as safe nor as efficacious as is commonly believed. Evolutionary biology posits that depression is an evolved adaptation that facilitated survival in our ancestral past and suggests that ADMs work by perturbing the homeostatic mechanisms that underlie the function that it evolved to serve (Andrews, Bharwani, Lee, Fox, & Thomson, 2015). Thus, there is reason to think that ADMs may have an iatrogenic effect that suppresses symptoms at the expense of prolonging the underlying episode. If true, that may account for the difficulty patients have discontinuing ADMs. That is the rationale behind a possible *iatrogenic effect for ADMs*.

In this article we address these three recent developments and their interrelated implications. Treatment selection algorithms can enhance the odds of getting patients better even before we improve on the existing interventions and, because they identify the subset of the population that shows a specific response to a given intervention, can be used to improve the power and precision of our tests of mediation. Task sharing and related strategies can be used to increase access to effective interventions for large segments of the world's population that are currently untreated for an eminently treatable but debilitating disorder. Evolutionary psychology suggests caution regarding how we treat disorders that may have evolved to serve a function; when multiple treatment options exist, it may be wise to choose the ones that enhance those underlying mechanisms rather than the ones that supersede them. We discuss each of these recent developments in turn.

Treatment Selection Indices: The Personalized Advantage Index

PROGNOSIS VS PRESCRIPTION

CBT can be as efficacious as ADM in the acute treatment of nonpsychotic unipolar patients when each is adequately implemented and the same is true for interpersonal psychotherapy (IPT; Hollon, Thase, & Markowitz, 2002). However, comparable overall response can mask considerable variability in response across individuals, and that variability often can be predicted by pretreatment characteristics. There are two types of predictive indices that are often confused in the literature. *Prognostic indices* are based on holding treatment constant (or ignore it altogether) while allowing individual differences to vary; they predict how someone will do at some future time in comparison to others (or who to select to make a treatment look good), but not what treatment is best for a given patient. *Prescriptive indices* (also known as moderator variables) hold individual differences constant and vary treatments experimentally (Fournier et al., 2009). Prescriptive indices can be used to select the best treatment for a given patient.

The problem with prescriptive indices is that we sometimes have too many. It is not clear what to do when multiple prescriptive indices point in different directions. In his classic monograph, Paul Meehl (1954) made a convincing argument that actuarial prediction usually beats clinical judgment when it comes to diagnostic assessments. Robert DeRubeis, who studied with Meehl at Minnesota, and his students at the University of Pennsylvania wanted to see if they could apply the same logic to generate treatment selection algorithms that combined multiple prescriptive indices in an actuarial fashion so as to identify the optimal treatment for a given patient. Working with data from a randomized controlled trial in which cognitive therapy (CT), an exemplar of CBT, was as efficacious as ADM (both produced response rates just under 60%) and each superior to pill-placebo (DeRubeis et al., 2005), they were able to identify several baseline indices that predicted differential response. Four of those prescriptive indices were ordinal in nature (only certain kinds of patients showed a differential response); patients with more prior ADM exposures did better in CT than they did in ADM (Leykin et al., 2007), as did patients who were married/cohabitating or unemployed or had more prior precipitants (Fournier et al., 2009). The fifth was disordinal (different kinds of patients showed opposite patterns of differential response); patients with personality disorders did better in ADM than they did in CT, whereas patients without personality disorders showed the opposite pattern (Fournier et al., 2008).

TREATMENT SELECTION ALGORITHMS

What the DeRubeis group did next was to combine those indices into regression equations that could be used to generate, for each patient, one prediction of

how they would do in CT and another prediction of how they would do in ADM (DeRubeis et al., 2014). They then plugged the scores for each patient on those five indices into each of those two equations to see how they would have done in each treatment and took the difference between the two as that patient's *Personalized Advantage Index* (PAI). When a patient's PAI was large, that indicated that they would be predicted to have done better in one treatment than the other, with the sign indicating the direction of that advantage. Since the patients had been randomized to the two conditions, they were able to compare how patients fared who got assigned to their indicated treatment (factual) versus those who did not (counterfactual); the magnitude of the difference between those patients who got what they should have gotten versus those who did not was as large as the drug-placebo difference (d = .58 vs d = .60). If models of this sort are successfully replicated across datasets or validated in prospective studies, it would mean that the mental health system could be improved (at least with respect to overall efficacy; other indices like safety remain to be explored), even without improving either modality.

The National Institute for Health and Clinical Excellence (NICE, 2004) defines "clinical significance" in terms of differences of three points or greater on the Hamilton Rating Scale for Depression (Hamilton, 1960). Only 60% of the sample had a PAI large enough to meet that criterion (divided roughly evenly across the two conditions); the remaining 40% of the sample would not have benefitted much from optimization but it would not have worked to their detriment (any non-zero score suggests a benefit). For the latter patients, other considerations would likely loom larger, such as convenience, side effects, or availability. While only one of the predictors was disordinal (personality disorder), it is possible to have differential response to each based solely on ordinal indices so long as different indices predict better response to different modalities.

It also is possible to have moderation in the context of a main effect for treatment. In the previous example both treatments were comparable in efficacy and outperformed pill-placebo. However, it is important to recall that even if one treatment works better than another (shows a main effect) that differential advantage does not necessarily hold for every patient. In the pharmacological literature, although there is little evidence that any one class of medications is more efficacious than another on average (Cipriani et al., 2018), there are long-standing indications that patients with atypical depressions do better on monoamine oxidase inhibitors (MAOIs) than they do on other ADMs (Hollon et al., 2002). Given that atypical depression is a less common variant of major depressive disorder, it is likely that this differential sensitivity is obscured in more heterogeneous samples and the same may prove true with respect to different types of psychotherapy. Examining individual patient data facilitates the test for moderation.

PROGNOSIS AS PREDICTION

Even when one treatment is consistently more efficacious than another (usually a less intensive intervention or a nonspecific control condition), there still may be variability in the degree of differential benefit that different individuals derive. The question then becomes, "Who should get priority for the stronger intervention?" if resources are limited. This is the province of *stratified medicine* (Cohen & DeRubeis, 2018). In such instances it is usually preferable to start by building a single prognostic algorithm ignoring treatment condition (likely few prescriptive indices) and then look to see if the differentially intensive treatments differ more from one another at some points on the prognostic continuum than they do at others (Forand, Huibers, & DeRubeis, 2017). In essence, this strategy searches for moderation after the fact with respect to a single multivariate prognostic continuum. As described by Cohen and DeRubeis (2018), Lorenzo-Luaces and colleagues applied this approach to a randomized controlled trial with very modest treatment effects (van Straten, Tiemens, Hakkaart, Nolen, & Donker, 2006) and found that patients with poor prognoses were more likely to show differential benefit from the high-intensity treatment than patients with good prognoses (Lorenzo-Luaces, DeRubeis, van Straten, & Tiemens, 2017). In essence, they were able to identify those patients who most needed the more intensive treatment.

MACHINE LEARNING AS A METHOD

The treatment selection literature is still evolving and there is no clear consensus as to what methodological approach works best in any given situation (Petkova et al., 2017). What is more likely is that one approach will work better in one situation and a different one in others depending on the degree of differentiation between the treatments and the success in identifying potential moderators. What is clear is that machine learning can amplify our ability to separate the predictive signal from noise in multivariate data (Kessler et al., 2017). Machine learning essentially recognizes patterns in a larger data set and can handle nonlinear relations and multivariate interactions among the potential predictors. The risk is that such

models will over-fit the data and generate selection algorithms that are difficult to replicate, but there are strategies that can be used to mitigate that risk (Cohen & DeRubeis, 2018).

Statisticians have long warned about the risk of looking for treatment effects in subpopulations in the absence of patient-by-treatment interactions (Pocock, Assmann, Enos, & Kasten, 2002). At the same time, tests for interaction effects are notoriously underpowered and progress in the field can be delayed unduly if such rules are applied in an overly rigid fashion. There was spirited debate about the propriety of reporting a severity-by-treatment interaction not specified *a priori* in the National Institute of Mental Health Treatment of Depression Collaborative Program (NIMH TDCRP: Elkin et al., 1989). The effect was reported and subsequent trials have repeatedly replicated that effect; only patients with more severe depressions separate from nonspecific controls with respect to either CBT (Driessen, Cuijpers, Hollon, & Dekker, 2010) or ADM (Fournier et al., 2010), although it does not moderate differences between CBT versus ADM (Weitz et al., 2015). Had the more rigid rule been followed, this instance of moderation would have gone unreported and subsequent investigators would not have known where to look. Cohen and DeRubeis (2018) describe numerous strategies that can be applied to guard against overfitting that greatly increase the odds of replication.

SUMMARY

Applying machine learning to large data sets ("big data") to generate treatment selection algorithms promises to revolutionize the field (Gillan & Whelan, 2017; Kessler, 2018). Being able to find the best treatment for a given patient will allow us to make health care delivery more efficient even in the absence of improving any of the existing interventions. That being said, it also will help us improve the quality of our treatments. As Kazdin (2007) first observed, moderation always implies differential mediation. What that means is that if different patients respond differentially to different interventions, then they must be responding to different mechanisms. The upshot is that we can do a more powerful job of testing for mediation if we differentiate those patients who show a specific response to a given intervention from those who do not. In effect, whenever there is moderation we have moderated mediation, and taking that into account will increase the likelihood of detecting causal mechanisms (MacKinnon, Fairchild, & Fritz, 2007). Moreover, "depression" is likely a catchall term for a number of heterogeneous conditions that differ in their underlying causes. Detecting moderated mediation can facilitate the search for natural phenotypes reflecting different underlying causal structures.

Global Mental Health: Task Sharing to Close the Treatment Gap

CLOSING THE TREATMENT GAP

Common mental disorders like depression and the closely related anxiety and stress disorders are the leading causes of disability worldwide (Whiteford et al., 2013). The vast majority of the world's population lives in LMICs where access to effective treatments is largely nonexistent and trained professionals are scarce. Closing this treatment gap is one of the primary goals of global mental health. As described by Singla and colleagues (2017), great strides are being made by *task sharing* or training nonspecialist providers (NSPs) to deliver effective interventions in a brief and time-limited fashion that has the promise of increasing access to large numbers of people who currently do not have access to treatments that work. NSPs reflect the context, varying from peers, community health workers, nurses and teachers (Singla et al., 2017). Basic treatments spanning interpersonal, cognitive and behavioral elements are high on the list of interventions that have been shown to be effective.

CULTURALLY ADAPTED BEHAVIORAL ACTIVATION

One recent example comes from a trial conducted in India that asked whether NSPs with no prior professional training could deliver a culturally adapted version of behavioral activation (BA) in a manner that is brief yet efficacious in a general practice setting (Patel et al., 2014). BA is a purely behavioral version of CBT that focuses on increasing activities intended to secure reinforcement, reducing avoidance behaviors, and minimizing rumination. In that trial (Patel et al., 2017; Weobong et al., 2017), a total of 495 participants who met criteria for moderate to severe depression were randomized to either enhanced usual care (EUC) that consisted of letting the primary care physician know that the patient was depressed and providing information regarding possible medication treatments or the addition of six-to-eight sessions of the Healthy Active Program (HAP), a culturally adapted version of BA.

To make the treatment more accessible to these individuals, cultural adaptions included home-based delivery, use of pictorial patient resource materials, strategies to encourage involvement of a significant other in treatment (Chowdhary et al., 2016), and training lay counselors to conduct peer supervision as reliably as expert mental health

specialists (Singla et al., 2014). In addition, the delivery of the core intervention was condensed from normal 20- to 24-session format used in efficacy studies in the West (Dimidjian et al., 2006) to a 6- to 8-session protocol. Lay counselors in the HAP condition with no prior professional training in mental health were provided 3 weeks of workshop training and 6 months of supervised clinical practice with actual patients. Those who passed minimal competence standards served as therapists in the trial.

In brief, HAP was found to be superior to EUC at the 3-month posttreatment assessment (Patel et al., 2017), and these gains were largely maintained through 12 months postrandomization (Weobong et al., 2017). Nearly twice as many participants met criteria for remission at the end of treatment (64% vs 39%) and rates of remission were largely maintained across the subsequent follow-up with some continued improvement in the EUC condition (63% vs 46%). We take this to mean that HAP as delivered by NSPs was efficacious in the treatment of acute depression and that this effect endured over time following treatment termination. In a chronic recurrent disorder like depression that is chronically undertreated in LMICs, these findings are impressive.

MECHANISMS AND ELEMENTS

That is not all. The study showed that patient-reported activation at 3 months mediated the intervention effects on depression outcomes at 12-months postenrollment. This meant the intervention worked through the behavioral activation model as intended and theorized. Furthermore, although only about a fifth of the sample reported intimate partner violence at intake, rates were cut in half by HAP (a nonsignificant trend). In a traditional rural culture that does not always value women, this finding was as impressive as it was unexpected. HAP not only encourages participants to become more active in pursuit of possible reinforcements, it also addresses avoidance and provides training in interpersonal assertion. The most effective interventions in LMICs tend to include common elements like nonspecific engagement and specific domains of cognitive, behavioral, emotional, and interpersonal elements (Bass et al., 2013). Global mental health is already moving down a track recently called for in HICs (Hofmann & Hayes, in press); the emphasis is less on "brand name" therapies and more on a common set of core elements that cut across diagnostic boundaries (Bolton et al., 2014; Murray et al., 2014). Not having an encrusted professional class may turn out to be a blessing for LMICs since there is nothing to impede the introduction of efficacious treatment elements in a truly transdiagnostic fashion. Task sharing also may prove beneficial in HICs where only 20% of the depressed receive minimally adequate treatments for depression (Thornicroft et al., 2017). A growing trend is to address the issue of accessibility to effective psychological treatments in HICs such as the United Kingdom (UK), United States (US), and Canada (Hoeft, Fortney, Patel, & Unützer, 2018).

INTEGRATED INTERVENTIONS

In another relevant trial, a parenting intervention that integrated interpersonal and behavioral elements was found to reduce rates of maternal depressive symptoms and improve child cognitive and language development scores in children aged 0–3 relative to a minimal treatment control (the normative nonintervention) in rural Uganda (Singla, Kumbakumba, & Aboud, 2015). Combined with psychosocial stimulation for the child, specific mother- and father-only sessions focused on the key message of "love and respect" to improve the parent's relationship with oneself, his or her child, and their spouse. Following a social cognitive learning theory model, participants were taught basic communication, emotional regulation, behavioral activation strategies, and parenting skills. These skills are neither complicated to teach nor to learn, but they made a real difference in their lives of the participants and their children. These effects were mediated by perceived support and psychosocial stimulation, which in turn improved maternal depressive symptoms and facilitated child development.

SUMMARY

There is growing evidence that task-sharing of simple (but not simplistic) interventions, largely behavioral with an interpersonal bent and delivered by NSPs with minimal training and supervision, can go a long way to reducing the treatment gap in LMIC countries; what works in rural India and sub-Saharan Africa also can work with the rural poor in eastern Tennessee or immigrant populations in inner-city Toronto. What we learn in global mental health can not only improve the lives of countless people in LMICs but also help improve our interventions by highlighting the common elements of efficacious treatments that may serve as the treatment's underlying mechanisms.

Is CBT Enduring or ADM Iatrogenic?

ADM "ÜBER ALLES"?

We now turn our attention to our third question, as to whether CBT is enduring or ADM iatrogenic. There has been a virtual explosion in the use of ADMs since the introduction of the SSRIs in the early 1990s. The reason for this explosion was that

general practitioners (GPs) felt safe in prescribing them; the SSRIs are not lethal in overdose like the earlier tricyclic antidepressants (TCAs) and do not require complex dietary restrictions like the MAOIs. As shown in Figure 1, before the introduction of the SSRIs, depressed patients in the US were twice as likely to be treated with psychotherapy than with ADM (Olfson, Marcus, Druss, & Pincus, 2002), but since their introduction those proportions have totally reversed, largely due to GPs feeling safe to prescribe SSRIs (Marcus & Olfson, 2010).

However, the SSRIs may neither be as safe nor as efficacious as is commonly believed. There is no question that ADMs are efficacious in the reduction of acute distress (Cipriani et al., 2018), but their apparent efficacy has been inflated by publication bias (Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008) and they only show a "true drug effect" (separate from placebo) among the third of patients with the most severe depressions (Fournier et al., 2010). The same is true for psychotherapy with respect to publication bias (Driessen, Hollon, Bockting, Cuijpers, & Turner, 2015) and moderation by severity (Driessen et al., 2010), but side effects in CBT involve improved functioning in interpersonal relationships like the reduction in intimate partner violence in the HAP trial (Patel et al., 2017) and greater return to work among the unemployed in the comparison of CT versus ADM previously described (Fournier, DeRubeis, Amsterdam, Shelton, & Hollon, 2015).

IS CBT ENDURING?

That being said, perhaps the major advantage that CBT has over ADM is that the psychosocial interventions appear to have an enduring effect that medications simply do not have; patients treated to remission with CBT are only half as likely to relapse (the return of symptoms associated with the treated episode) following treatment termination as patients treated to remission with ADM and no more likely to relapse than patients kept on continuation medication (Cuijpers et al., 2013). Moreover, those two trials that have extended treatment-free follow-ups long enough to test for recurrence (the onset of wholly new episodes in recovered patients) have found similar enduring effects for both CT (Hollon et al., 2005) and BA (Dobson et al., 2008). In a chronic recurrent disorder, that is major advantage.

The problem is that the bulk of the support for this enduring effect is based on trials comparing prior CBT to prior ADM with the assumption that ADM exposure is benign and has no lingering negative effects. In a provocative treatise published nearly a decade ago, Robert Whitaker, an investigative journalist, challenged this assumption (Whitaker, 2010). The basic question that he asked was whether the quality of mental health had improved since the introduction of the psychiatric medications in the 1950s and his answer was that it most assuredly had not. Rates of psychiatric disability have skyrocketed, the trajectories of many disorders appear to have "coarsened," patients are having a harder time

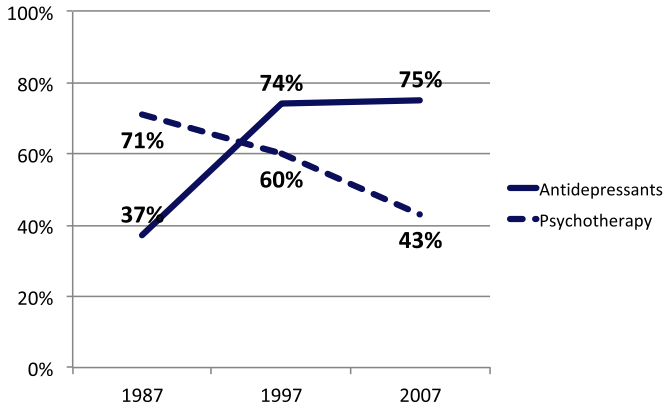

FIGURE 1 National Trends in Outpatient Treatment in Depression Psychotherapy is as efficacious as and more enduring than medications with an enduring effect that cuts risk for relapse by half following treatment termination yet still has been losing market share to medications over the last three decades since the introduction of the SSRIs. Adapted from "National trends in the outpatient treatment of depression." M. Olfson, S. C. Marcus, B. Druss and H. A, Pincus, 2002, *JAMA, 287,* 203-209 and "National trends in the treatment for depression from 1998 to 2007." S. C. Marcus and M. Olfson, 2010, *Archives of General Psychiatry, 67(12),* 1265-1273.

getting off of medications without relapsing, and new syndromes, such as pediatric bipolar disorder, have appeared that had not been seen before. There are other ways to account for each of these observations, but each requires a separate explanation and Whitaker needs but one: that psychiatric medications suppress symptoms at the expense of worsening the course of the underlying disorder. In essence, we are "robbing Peter to pay Paul"—buying short-term symptom relief at the price of worsening the underlying disorder.

DEPRESSION AS EVOLVED ADAPTATION

Evolutionary theory suggests that depression may be an evolved adaptation (like anxiety or pain) that serves a functional purpose (Andrews et al., 2015). There is reason to think that ADMs (SSRIs included) may suppress symptoms via mechanisms that increase the risk for relapse following discontinuation, making them very hard to stop (Andrews, Kornstein, Halberstadt, Gardner, & Neale, 2011). Moreover, naturalistic longitudinal follow-ups suggest that SSRIs may increase "all-cause" mortality by 30% for patients without heart disease (Maslej et al., 2017). CBT is thought to have an enduring effect that reduces risk for subsequent symptom return, but largely based on comparisons to ADM discontinuation (Cuijpers et al., 2013). The question then becomes whether CBT is truly enduring or ADM iatrogenic in prolonging the underlying episode.

MECHANISMS PARADOX

All the most widely prescribed ADMs work through one of two proximal mechanisms. The MAOIs block the degradation of the biogenic amines (serotonin, norepinephrine, and dopamine), whereas the SSRIs and TCAs all block reuptake by gumming up the transporters on the presynaptic neuron. In either case, all ADMs increase the amount of neurotransmitter in the synapse and that is thought to increase transmission in that neurotransmitter system. The SSRIs are relatively selective for serotonin (although fluoxetine affects norepinephrine at higher doses), whereas TCAs block reuptake of both serotonin and norepinephrine and MAOIs inhibit the degradation of all three biogenic amines including dopamine. Current thinking in psychiatry is that the ADMs work by correcting a functional deficit in neurotransmitter levels with serotonin being the prime suspect because all the major classes of ADM affect its levels. The notion then is that ADMs work by increasing extracellular levels of serotonin so as to affect downstream mechanisms. The problem with this formulation is that depression does not show a deficit in extracellular serotonin; if anything, there is excess (Andrews et al., 2015).

PARADOX RESOLVED

Andrews, an evolutionary biologist, and his colleagues (2015) resolved this paradox by going to the animal literature. The short-term effect of putting SSRIs into the system is to block reuptake and increase the amount of extracellular serotonin but the longer-term effect that kicks in after several days is to inhibit serotonin synthesis in the presynaptic neuron and reduce sensitivity in the post-synaptic neuron. In essence, increasing levels of extracellular serotonin via using SSRIs to block reuptake leads internal homeostatic regulatory mechanisms to reduce the amount of serotonin produced and turn down transmission through the system. Prescribing SSRIs is analogous to holding a match to a thermostat to turn the furnace down; they likely work in the opposite fashion than currently understood.

RUMINATION RESOLUTION

From the perspective of evolutionary biology, depression is not so much a disorder as an evolved adaptation that serves to increase the odds that the gene line will survive, much like anxiety or pain (Andrews & Durisko, 2017). Serotonin is an evolutionarily ancient neurotransmitter that has energy distribution as its major function. Clinical depression has striking similarities to infection and starvation; infection is accompanied by lassitude and loss of interest in appetitive pursuits and the same is true for starvation. It is serotonin that reallocates the distribution of energy away from hedonic pursuits and toward increased immune system function during infection and away from muscle tissue and toward the maintenance of vital organs like the heart and the brain during starvation. What serotonin does during clinical depression is to reallocate energy to complex and perseverative thinking (aka rumination; Andrews et al., 2015).

Why rumination? Our evolutionary ancestors lived in small family bands that consisted of about 25 members. Survival depended on staying in the good graces of the group and that was especially the case for females and their infant offspring. According to the *analytic rumination hypothesis*, complex interpersonal problems that led to ostracism from the group would constitute a virtual death sentence and the best way to solve such a problem was to stay focused on it (ruminate) until a solution could be reached (Andrews & Thomson, 2009). The best-established psychosocial interventions either target interpersonal problems (IPT) or facilitate more generic problem solving (CBT). It may well be that they speed along the same processes that worked in

our evolutionary past to resolve complex social problems.

Two things are striking about this hypothesis. First, the raphe nucleus is a collection of cell bodies deep in the brain stem that is the source of all serotonin used as a neurotransmitter in the brain. As shown in Figure 2, when the raphe nucleus fires it enervates regions of the brain that produce all of the major symptoms of depression that are shared by sickness behavior and starvation, including anhedonia, and one that is not, rumination (Andrews et al., 2015). The second is that unipolar depression is about twice as common in women as it is in men and this gender-linked difference does not emerge until early adolescence when primates reach sexual maturity. Women ruminate more than men, whether depressed or not, and are more likely to talk their way through an interpersonal problem than resort to violence as men are prone to do (Hankin et al., 2015).

OPPOSITIONAL PERTURBATION

Depression has long been thought to be an episodic disorder, with any given episode likely to resolve on its own, even in the absence of treatment (spontaneous remission), but prone to recurrence (the onset of wholly new episodes). While it is unknown what mechanisms underlie spontaneous

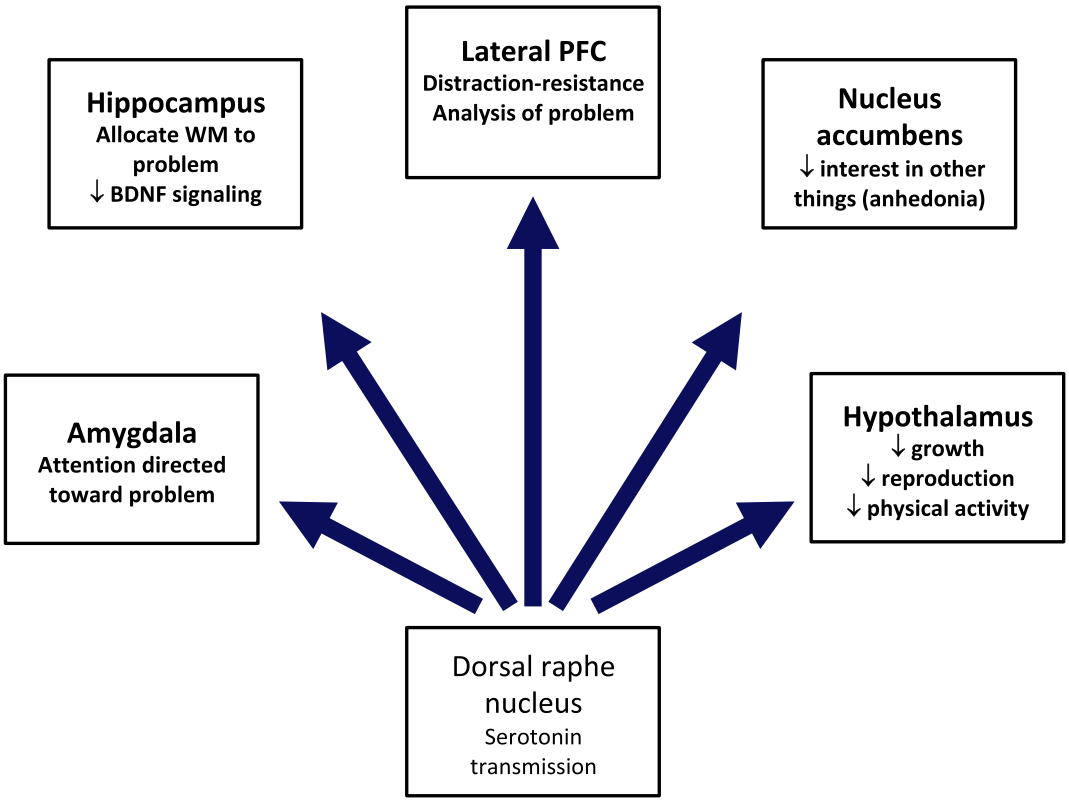

FIGURE 2 Does Depression Have an Adaptive Function?
Serotonin evolved to regulate energy so as to keep organism focused on solving the problem at hand (analytic rumination) rather than using resources for growth and pursuit of rewards. The main projection regions for elevated serotonin transmission in rodent models of melancholia and the hypothesized effects on symptoms in humans. Increased serotonin transmission coordinates multiple processes that promote sustained processing of the problem that triggered the episode: (1) Transmission to the amygdala directs attention to the problem that triggered the episode. (2) Transmission to the hippocampus promotes changes in synaptic plasticity involved in allocating working memory to the triggering problem, and reduces BDNF signaling. (3) Transmission to the lateral PFC is involved in processing of the problem and promoting the resistance to distracting stimuli. (4) Transmission to the nucleus accumbens produces anhedonia that reduces the interest in attending to alternative stimuli. (5) Transmission to the hypothalamus downregulates other energetically expensive processes (growth and reproduction) that could draw limited resources away from processing of the problem, which probably contributes to many psychomotor symptoms (e.g., reduced eating and sexual activity, social withdrawal, lethargy). Reprinted from "Is serotonin an upper or a downer? The evolution of the serotonergic system and its role in depression and the antidepressant response." P. W. Andrews, A. Bharwani, K. R. Lee, M. Fox, and J. A. Thomson, Jr. 2015, *Neuroscience and Biobehavioral Reviews, 51,* p. 167. Copyright 2008 by Elsevier.

remission, it is likely that these internal homeostatic regulatory mechanisms revolve around the biogenic amines. It is possible that putting medications on board "hijacks" this homeostatic regulatory system and locks it in a "steady state." As shown in Figure 3, Andrews and colleagues (2011) posit that ADMs lock the homeostatic regulatory system in place and create a state of "oppositional perturbation" that is ready to spring back whenever medications are withdrawn.

What this model would predict is that the more an ADM perturbs the underlying neurotransmitter systems the greater the likelihood of relapse once it is discontinued. As shown in Figure 4, that is exactly what happens (Andrews, Thomson, Amstadter, & Neale, 2012). Patients who remit on pill-placebo are only half as likely to relapse following discontinuation as patients who remit on SSRIs (serotonin only). Relapse rates go up for the serotonin-norepinephrine reuptake inhibitors (SNRIs) and go higher still for the TCAs that perturb both serotonin and norepinephrine. The highest rates are found for the MAOIs that also

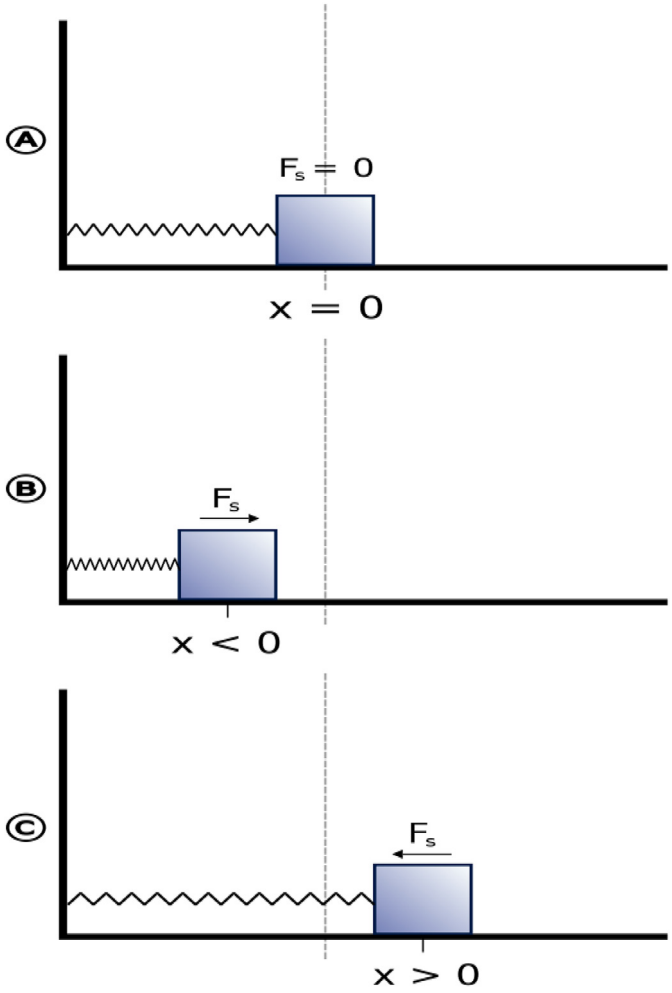

FIGURE 3 Oppositional Perturbation
Like a spring, synaptic serotonin has an equilibrium level (Panel A). When one takes an antidepressant (Panel B), the drug perturbs the system from equilibrium. Just as a spring resists a perturbation by producing an opposing force (F_s), the brain produces an opposing force (proportional to the strength of the drug) that attempts to bring synaptic serotonin back to equilibrium. When the drug is discontinued (Panel C), the oppositional force causes an overshoot that is proportional to the strength of the drug. Adapted from "Blue again: Perturbational effects of antidepressants suggest monoaminergic homeostasis in major depression," P. W. Andrews, S. G. Kornstein, L. J. Halberstadt, C. O. Gardner and M. C. Neale, 2011, *Frontiers in Psychology, 2,* 159. The image is in the public domain: https://commons.wikimedia.org/wiki/File:Harmonic_oscillator.svg

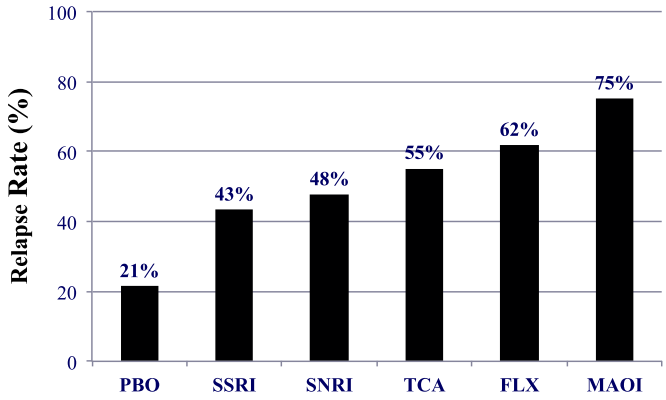

FIGURE 4 Risk of Relapse Following Medication Discontinuation
The extent to which a given medication class perturbs the underlying neurotransmitter systems as assessed in rodents predicts the likelihood of relapse following medication withdrawal in humans. After discontinuation, all ADMs have at least twice the risk of relapse as pill-placebo. Adapted from "Primum *non nocere*: an evolutionary analysis of whether antidepressants do more harm than good." by P. W. Andrews, J. A. Thomson, Jr., A. Amstadter, and M. C. Neale, 2012), *Frontiers in Psychology, 3,* 117.

perturb dopamine. Fluoxetine appears to be an outlier; however, although an SSRI it has an effect on norepinephrine at higher doses. In effect, evolutionary biology anticipated the extent to which ADM perturbation in rodents predicts relapse in humans.

SUMMARY

The upshot is that a plausible case can be made that the apparent coarsening (longer episodes with less complete remission) noted in human depression and the increasing difficulty getting patients off ADMs without triggering a relapse may be a consequence of putting them on ADMs in the first place. To the extent that this is true, it also calls into question whether CBT truly has an enduring effect or is simply free of any iatrogenic effect that the ADMs might possess. The question could be resolved by comparing patients treated to recovery in each modality to patients treated to recovery on pill-placebo (PLA); if CBT is prophylactic then patients who recover in that modality should be less likely to recur than patients who recover on PLA, whereas if ADM is iatrogenic then patients who recover on that modality should be more likely to recur than patients who recover on PLA. Since either CBT or ADM should bring more (and tougher) patients to recovery than PLA (by about 25%), comparisons among recovered patients should be biased against the active modalities. However, something akin to the treatment selection algorithm (aka propensity analyses) can be used to exclude those patients who show a specific response to either active modality from comparisons to PLA.

Conclusions

This article described three recent advances in the treatment of depression. First, machine learning can be used to generate *treatment selection algorithms* to identify the optimal treatment for a given patient. This not only has the potential to improve outcomes by making mental health care treatment more efficient, but also to make tests of mediation more specific. Second, *global mental health* is using task sharing to train NSPs to provide brief interventions based on transdiagnostic elements essential to efficacious treatments to close the treatment gap in LMICs. The lessons learned reverberate to treatment delivery in HICs. Finally, there is reason to suspect that ADMs, as efficacious as they are, may have an *iatrogenic effect* that suppresses symptoms at the expense of prolonging the underlying episode. The optimal strategy may be to start patients on CBT unless they are predicted to do better over time on an ADM by a treatment selection algorithm. Each of these innovations has the potential to improve the quality and breadth of treatment; in aggregate they could be used to reduce the prevalence of depression worldwide.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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