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Evolutionary theory and the treatment of depression: It is all about the squids and the sea bass

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ABSTRACT

According to the analytical rumination hypothesis, depression is an evolved adaptation (like pain or anxiety) that served in our ancestral past to keep people focused on complex interpersonal problems until they could arrive at a resolution (spontaneous remission). If this is true, then those clinical treatments that most facilitate the functions that depression evolved to serve are likely to be more advantageous in the long run than others that simply relieve distress. For example, antidepressant medications may be efficacious in the treatment of depression but only work for so long as they are taken. They may also have an iatrogenic effect that prolongs the duration of the underlying episode. Cognitive and behavioral interventions are as efficacious as medications in terms of reducing acute distress and also appear to have an enduring effect that protects against the return of subsequent symptoms. However, the bulk of the evidence for this effect comes from comparisons to prior medication treatment and it remains unclear whether these psychosocial interventions are truly preventative, or antidepressant medications iatrogenic. A study is described that could resolve this issue and test evolutionary theory with respect to the purported role of rumination in bringing about spontaneous remission.

1. Introduction

Depression is the single most prevalent of the psychiatric disorders and the second leading cause of disease burden worldwide (Ferrari et al., 2013). Antidepressant medications (ADMs) are the most commonly used interventions for the treatment of depression (Jorm, Patten, Brugha, & Mojtabai, 2017) and the third most commonly prescribed medication class in the United States (Pratt, Brody, & Gu, 2017). ADMs are taken by 12% of the US population ages 18–85, with 85% of patients taking them for over two years and 25% for over ten years (Moore & Mattison, 2017). However, they only work as long as they are taken, and guidelines call for maintaining patients with chronic depression or a history of recurrence on ADMs indefinitely (American Psychiatric Association, 2010). Concerns have been raised about their long-term safety (Malm et al., 2016; Maslej et al., 2017) and there is reason to believe they have an iatrogenic effect that prolongs the life of the underlying episode and leaves patients at elevated risk for relapse whenever taken away (Andrews, Kornstein, Halberstadt, Gardner, & Neale, 2011).

Cognitive behavior therapy (CBT) can be as efficacious as ADMs if adequately implemented (DeRubeis et al., 2005; Dimidjian et al., 2006) and appears to have a long-term enduring effect not found for medications (Cuijpers et al., 2013; Dobson et al., 2008; Hollon et al., 2005). However, the bulk of the evidence for this enduring effect comes from comparisons to prior ADM following treatment termination and it remains unclear whether CBT is truly prophylactic or ADMs iatrogenic. We describe the logic behind each possibility and propose a study that could determine which if either is true.

2. Depression as an evolved adaptation

A case can be made that depression, like anxiety or pain, is an evolved adaptation that served a functional purpose in our ancestral past (Wakefield, 1992). Depression is highly prevalent, affecting up to 16% of the population in retrospective epidemiological surveys (Kessler et al., 2003). Cohort studies followed prospectively from birth suggest that the actual prevalence may be three times higher still with the bulk of the

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undetected those who do not become recurrent (Monroe, Anderson, & Harkness, 2019). Depression has its greatest incidence during adolescence and young adulthood, the time of life in our ancestral past when people started having babies (Hankin et al., 2015). That is an unusual temporal course for a "disease" to follow; most kill us in our first year of life or in our dotage. That alone would suggest to an evolutionary biologist that depression is an evolved adaptation and not an "illness" since the brain is not "broken", or even a "disorder". Breakdowns of biological systems or conditions that impair adaptive functioning should be extremely rare during the reproductive years.

If depression is an evolved adaptation, that raises two questions: 1) what function did it evolve to serve? Anxiety keeps you safe from harm while pain helps you avoid additional tissue damage, but what does depression do to increase reproductive fitness? And 2) are there unintended consequences of symptomatic treatments like ADMs? It is a basic principle of evolutionary medicine that any disruption of an evolved adaptation will degrade the quality of biological functioning (Nesse & Williams, 1994). Could use of ADMs have untoward consequences (Andrews, Thomson, Amstadter, & Neale, 2012)?

Several different evolutionary theories have been proposed to account for depression (Nesse, 2000). Theories include the facilitation of attachment (Bowlby, 1980), conservation-withdrawal in unpropitious circumstances (Engel & Schmale, 1972), disengagement from unobtainable goals (Klinger, 1975), elicitation of support from partners (Hagen, 1999), warding off attack following loss of status (Price, Sloman, Gardner, Gilbert, & Rohde, 1994), reducing risk of social exclusion (Allen & Badcock, 2003), and down-regulating positive affect in response to social threat (Gilbert, 2006). Any could be relevant but all likely would be the products of evolved adaptations.

For reasons we describe below, we are particularly interested in the notion that depression evolved in our ancestral past to facilitate analytical rumination (Andrews & Thomson, 2009). In the context of depression, rumination refers to recurrent and persistent thinking about a depressive episode and its circumstances (Smith & Alloy, 2009). Although rumination typically is considered to be an unproductive symptom of depression that interferes with problem solving and may even worsen the course of the episode (Nolen-Hoeksema, 2012), the analytical rumination hypothesis posits that it actually facilitates thinking through whatever problems brought about the depressive episode in the first place (Andrews & Thomson, 2009).

Thus, according to this hypothesis, complex social problems generate distress, which motivates a process of causal analysis. This process starts with a careful analysis of the causes of the problem(s) that led to the distress and the generation of solutions to bring about its resolution or to avoid future instances. Because this analysis helps to focus problem solving efforts on addressing the root causes of problems, causal analysis increases (but does not guarantee) the likelihood of finding a solution that in turn has the consequence of reducing the distress. A recent cross-sectional study assessed these two aspects of analytical rumination, causal analysis and problem-solving analysis, in clinical and nonclinical samples. Its results were consistent with this model: depressive symptoms predicted causal analysis, which predicted problem-solving analysis (Bartoskova et al., 2018) and a longitudinal trial found that problem-solving predicted subsequent reductions in depression (Sevcikova et al., 2020). In engineering terms, this "closed system" could provide an account of how spontaneous remission came about in ancestral times.

Depression typically is precipitated by negative or stressful experiences that can include interpersonal conflicts or reversals in achievement-related domains (Keller, Neale, & Kendler, 2007; Kendler et al., 1995; Lewinsohn, Hoberman, & Rosenbaum, 1988; Zisook & Shuchter, 1991). Social ostracism would have been lethal in our ancestral past since an isolated individual would have been picked off by predators or starved. Stressors in either the affiliative or achievement domains can still threaten important resources, status, or survival. They are also complex situations with no clear solutions and involve competing goals. Addressing these situations may require prolonged, uninterrupted thinking about their various components to identify why they are happening and to eventually arrive at the best course of action. Or if they are irreparable, causal and problem-solving analyses can help to prevent similar situations from re-occurring in the future (Andrews & Thomson, 2009). This is where analytical rumination comes in.

What sets the analytical rumination hypothesis apart from conventional clinical perspectives on rumination is its analytical component. The argument relies on the widely recognized distinction between two major information-processing styles (Evans & Stanovich, 2013). 'Type 1' processing tends to be fast, associative, and automatic, while 'Type 2' processing is slower, effortful, and rule based. It also places greater demands on working memory. Type 1 is usually the default style because it is quick, simple, and heuristic, while Type 2 processing is slower, attentionally demanding, and analytic. Type 2 is more likely to involve trade-offs because if limited time and attention are devoted to one matter, there is less available time and attention to devote to other matters. In various experiments, sadness has been shown to promote Type 2 processing (Forgas, 2013). Analyzing the causes of complex social problems may require prolonged Type 2 processing, which can explain why rumination is so persistent, distraction-resistant, and often accompanied by sadness, an emotional component of depression.

Depression is often comorbid with anxiety and fear, but the different affects call for different kinds of thinking to resolve different kinds of challenges. Whereas depression is often triggered by complex social problems that have already occurred (or continue to occur), anxiety represents a heightened state of vigilance regarding potential threats in the offing and fear represents a coordinated whole-body response to imminent risk. The premium in the latter is on a readiness for action (anxiety) or the action itself (fear) and Type 1 thinking predominates (Baron, Inman, Kao, & Logan, 1992). Better to respond to a "false alarm" than to fail to do so and become something else's lunch. Different affects coordinate different whole-body responses in response to different kinds of challenges, but they all coordinate a whole-body response that fits the demands of the specific challenge (Andrews, Maslej, Thomson, & Hollon, 2020).

There is considerable evidence that the underlying neurobiology of depression is designed to allocate additional energy to the brain. As depicted in Fig. 1, the raphe nucleus is a structure in the midbrain that contains the cell bodies for all neurons that use serotonin as a neurotransmitter. It projects to various regions of the brain that are all implicated in analytical rumination. Thus, heightened serotonin transmission to the amygdala, hippocampus, and lateral prefrontal cortex will increase the likelihood that the individual will direct attention to the source of the distress in a manner that takes up limited working memory and is resistant to distraction (for a detailed review of this evidence, see Andrews, Bharwani, Lee, Fox, & Thomson, 2015). This is a recipe for rumination. This process also draws energy away from hedonic pursuits (nucleus accumbens) and competing energetic demands (hypothalamus). Serotonin is an evolutionary ancient neurotransmitter and evidence from the animal literature suggests that it is largely responsible for energy allocation in response to different threats (Andrews et al., 2015). When faced with infection, energy is directed toward the immune system and when faced with starvation, energy is directed toward the maintenance of the vital organs. In melancholia, there is a general sense of malaise (dysphoria) and appetitive pursuits are shut down (anhedonia), but there is an increment in rumination. There must be a reason for this to occur.

3. Temporality in depression

Whereas phobias tend to be specific to particular stimuli but stable over time, depression tends to be episodic in nature but stable across situations. Most episodes also are self-limiting. That is, they go away even in the absence of treatment, referred to as spontaneous remission. Fig. 2 depicts a conceptual model first proposed by Kupfer (1991) and

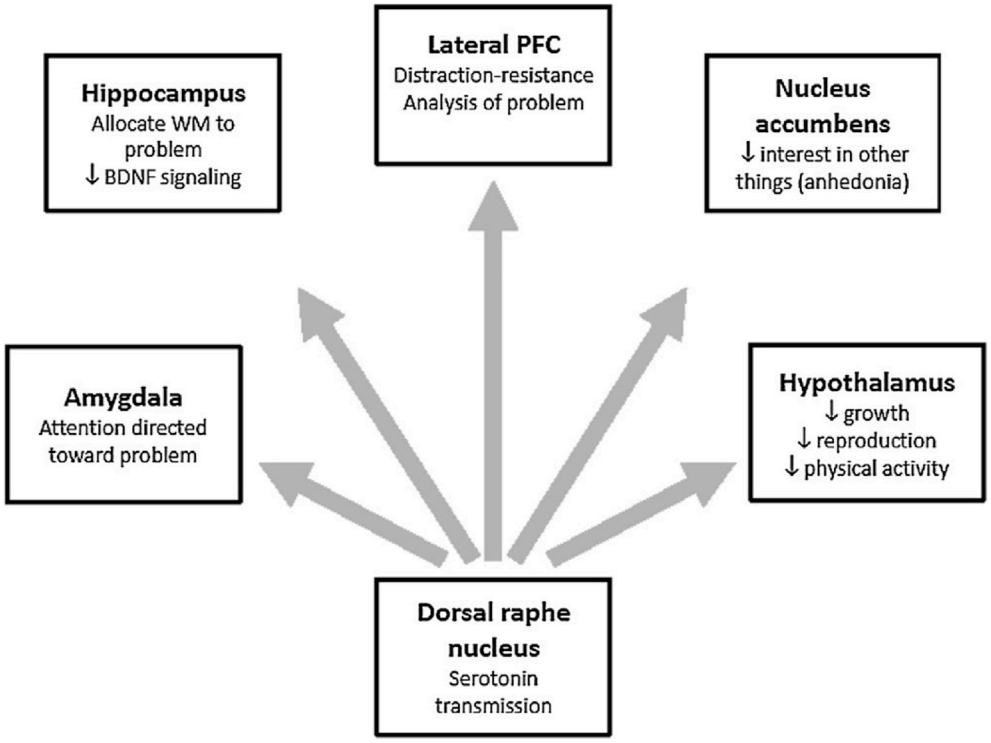

Fig. 1. The main projection regions for elevated serotonin transmission in rodent models of melancholia and the hypothesized effects on symptoms: Increased serotonin transmission coordinates multiple processes that promote sustained processing of the problem that triggered the episode: (1) Transmission 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, which reduces interest in attending to alternative stimuli. (5) Transmission to the hypothalamus downregulates other energetically expensive processes (growth, reproduction) that could draw limited resources away from processing the problem, which probably contributes to psychomotor symptoms (e.g., reduced eating and sexual activity, social withdrawal, lethargy).
Reprinted with permission from "Is Serotonin an Upper or a Downer? The Evolution of the Serotonergic System and its Role in Depression and the Antidepressant Response," by P. W. Andrews, A. Bharwani, K. R. Lee, M. Fox, & J. A. Thomson Jr, 2015, *Neuroscience and Biobehavioral Reviews, 51,* p. 167.

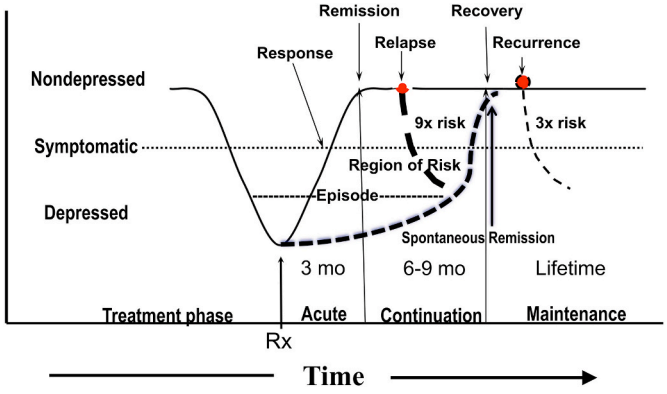

Fig. 2. The 5 Rs of Depression. This modified figure was inspired by the consensus definitions developed by the MacArthur Network chaired by David Kupfer and published (sans figure) by Frank et al., 1991 in the *Archives of General Psychiatry*. ***Response*** refers to "better" (typically a 50% reduction in scores from baseline) whereas ***remission*** refers to fully "well" (asymptomatic); ***relapse*** refers to a return of the treated episode (which is presumed to have not yet run its course); ***recovery*** refers to the end of the underlying episode; and ***recurrence*** refers to the onset of a new episode. The risk for relapse (before the underlying episode has run its course) is presumed to be greater than the risk for recurrence by a factor of at least three, which is why prescribing clinicians are encouraged to keep remitted patients on medications for 6–12 months following remission. After that point patients can (perhaps) be brought off medications. However, patients with a history of chronic or recurrent depression (85% of patients in clinical settings) are increasingly kept on medications for as long as they maintain their remission and they can tolerate their medications.
Adapted with permission from "The long-term treatment of depression," by D. J. Kupfer, 1991, *Journal of Clinical Psychiatry, 52(Suppl 5),* 28–34.

subsequently adopted by both the MacArthur group (Frank et al., 1991) and the American College of Neuropsychopharmacology (Rush, Kraemer, et al., 2006) that has guided recommended pharmacological practice for the last quarter century. We do not agree with every aspect, but it does represent how psychiatry thinks about depression.

In this model, referred to in the field as the "5 Rs model of depression", people become increasingly symptomatic until they cross some diagnostic threshold and are said to be in episode. At whatever point ADMs are begun (depicted by "Rx" at the bottom of the figure), most people will start to feel better within a matter of weeks (as depicted by the solid line). A partial reduction in symptoms is referred to as **response**, whereas continued improvement until one is no longer symptomatic is referred to as **remission**. Remission is considered the proper goal of treatment and most psychiatrists will "dose to remission", raising dosage rapidly to its maximally tolerated level and combining, augmenting, or switching ADMs until remission is achieved (Rush, Trivedi, et al., 2006).

The dashed line in the figure indicates the natural course of the untreated episode (referred to subsequently as the "underlying episode"). Most people will remit spontaneously even if left untreated, but they will remain symptomatic longer than if medications are prescribed (Whiteford et al., 2013). Given that most episodes will remit spontaneously a question can be raised as to why treat at all. The answer is that depression is a miserable experience that typically takes 6–9 months to remit, whereas treatment can bring about symptomatic relief in a matter of weeks. Many wounds can heal on their own, but most physicians will speed the process along with stitches.

If ADMs are discontinued within the expected duration of the underlying episode (the region of risk between the dashed and solid lines), patients are thought to be more likely to experience a return of symptoms (presumably falling back into the treated episode), referred to as a **relapse**, than if ADMs are continued until after the episode has run its course, at which point the patient is said to be in **recovery**. Anyone who has ever been depressed is more likely to experience the onset of a new episode than someone who has never been depressed; this is termed a **recurrence.** Clinical practice guidelines recommend that ADMs be continued for up to a year past the point of remission in order to prevent relapse (the return of a treated episode) and that they be maintained indefinitely among chronic or recurrent patients to protect against recurrence (the onset of new episodes) (American Psychiatric Association, 2010).

What does it mean to be "in episode"? Although it is not always explicit, this model introduces an interesting conceptual distinction that did not exist before the advent of the ADMs. According to the DSM, a person can be said to be "in episode" when he or she exhibits a sufficient number of symptoms to meet criterion for major depression and no longer "in episode" once he or she no longer does. However, the logic of the 5 Rs model implies that patients remain at elevated risk for symptom return (relapse) for an extended period time after they are in "remission" and no longer manifestly symptomatic. The MacArthur Group put it thusly: "Implicit in the distinction between a relapse and a recurrence … is the hypothesis that relapse represents the return of the symptoms of a still ongoing but symptomatically suppressed episode, while a recurrence represents an entirely new episode …. " (Frank et al., 1991, p. 853). This implies that the underlying episode lives on even after the patient is no longer manifestly symptomatic.

The notion that a patient can still be "in episode" despite an absence of symptoms is why patients are kept on medications for an extended period of time (e.g., up to a year) following remission. We think this means that psychiatry has come to distinguish between the "manifest episode" (a sufficient number of observable symptoms to justify a DSM diagnosis) versus the "underlying episode" (in which neural processes are still in play that would cause the symptoms to reemerge if not suppressed by ADM).

The ACNP Task Force report is more explicit: "Consequently, the distinction between remission and recovery depends on the interval following symptom reduction that reflects the resolution of the ***underlying neurobiology*** of the MDE [major depressive episode] …. A corollary is that the probability of a return to a symptomatic state is much higher for patients who have only achieved a brief period of remission as compared to those who have reached recovery" (Rush, Kraemer, et al., 2006, p. 1843). The Task Force notes that the distinction between remission and recovery may not be valid if risk does not decline over time, but goes on to state: "In theory, recovery implies that the disease processes that are immediately involved in the expression of the syndrome are arrested … such that the syndromal expression is no longer present. On the other hand, underlying vulnerability to subsequent syndromal episodes may remain …. recovery is not recovery from the illness but from the last MDE …. " (Rush, Kraemer, et al., 2006, p. 1847).

Prior to the advent of the ADMs there was no need to distinguish between the "manifest" versus the "underlying" episode (or remission versus recovery) since they were one and the same. Whatever the initial cause, if the neurobiology that maintained the episode was still running its course then you were symptomatic since symptoms could not be suppressed. By contrast, ADMs may suppress the expression of the "manifest episode" without allowing the "underlying episode" to run its course; that is, without resolving the underlying neurobiology that would otherwise lead to the expression of symptoms. Thus ADMs, by their nature, may be palliative (i.e., suppressing symptoms) but not curative (i.e., not resolving the underlying processes that drive the episode).

4. Are antidepressant medications iatrogenic?

According to the 5 Rs model depicted in Fig. 2, ADMs may be palliative at best: they suppress symptoms for only as long as they are taken but do nothing to shorten the course of the underlying (biologic) episode. It is also possible that they are iatrogenic: they may worsen the underlying episode by interfering with the normal homeostatic mechanisms that would otherwise cause the underlying episode to spontaneously remit. The conventional monoamine hypothesis posits that ADMs work by correcting a "deficit" in biogenic amines, either blocking reuptake of a neurotransmitter into the presynaptic neuron, as is the case of the selective serotonin reuptake inhibitors (SSRIs) and the older tricyclic antidepressants (TCAs), or by inhibiting enzymatic degradation, as is the case of the even older monoamine oxidase inhibitors (MAOIs) (Belmaker & Agam, 2008). The short-term consequence of taking any of these medications is to increase the amount of extracellular neurotransmitter in the synapse. This is believed to be the proximal mechanism that triggers causal processes downstream in the brain that in turn then leads to symptom relief (Duman, Heninger, & Nestler, 1997).

The problem with this explanation is that there is no functional deficit in serotonin in the brains of persons who are depressed and certainly no deficit in their synapses (Andrews et al., 2015). According to the most direct evidence available, there may even be an excess of serotonin. To assess serotonin levels in the brains of patients with major depression before and after treatment with an SSRIs, Barton et al. (2008) put a catheter in the internal jugular vein, the large vessel in the neck that brings blood back from the brain to the heart so as to sample the blood flowing directly from the brain. They found that 5-HIAA (the major metabolite of intracerebral serotonin) is elevated in unmedicated patients but did not differ from controls in patients after SSRI treatment. This indicates an excess (not a deficit) of serotonin in depressed patients and a decrease (not an increase) in serotonin with SSRI treatment. These apparently paradoxical results are congruent with at least five other studies having shown an improvement in depressive symptoms associated with a reduction in 5-HIAA in the cerebrospinal fluid (CSF) of patients with major depression treated with various SSRIs (Barton et al., 2008).

The resolution of this paradox comes from looking at what happens in animals or humans when they are given SSRIs. Extracellular serotonin increases initially to levels up to four times those found in nature before internal homeostatic mechanisms kick in and shut the system down; synthesis in the presynaptic neuron is inhibited and the sensitivity of post-synaptic receptors is turned down (Andrews et al., 2015; Hyman & Nestler, 1996). In effect, taking an SSRI drives the level of extracellular serotonin so high that it triggers homeostatic mechanisms to push back so as to turn the system down. This is analogous to holding a match up to a thermostat to turn a furnace down and the antithesis of the commonly held belief about precisely how ADMs are thought to work.

This process does suppress symptoms in most patients, although some may exhibit a sudden and rapid loss of response called tachyphylaxis (Targum, 2014) and others may develop a progressive resistance to the effects of ADMs such that they are less likely to respond across subsequent trials (Leykin et al., 2007). Most relevant to our current discussion is something called "oppositional tolerance" that may apply to all (Andrews et al., 2011). With oppositional tolerance, depressive symptoms are held in check as long as patients continue to take the ADMs that continue to drive the counter-regulatory

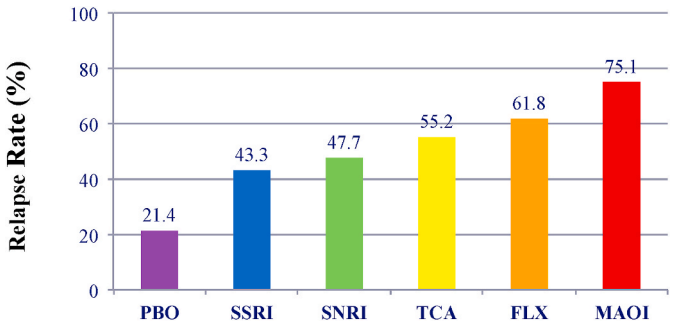

Fig. 3. Risk of Relapse Following Discontinuation by Medication Class: The more a medication class perturbs the underlying neurotransmitter systems the greater risk of relapse after discontinuation. Patients treated to remission on pill-placebo (PBO) that affects none of the biogenic amines have only about one chance in five of relapsing after treatment termination, whereas that risk more than doubles for patients treated to remission on selective serotonin reuptake inhibitors (SSRI) that perturb serotonin only and goes up higher still on the serotonin norepinephrine reuptake inhibitors (SNRI) and tricyclic antidepressants (TCA) that also perturb norepinephrine. (Although fluoxetine (FLU) typically is considered an SSRI it also perturbs norepinephrine at higher doses.) Monoamine oxidase inhibitors (MAOI) perturb dopamine as well as the other two biogenic amines (serotonin and norepinephrine) and have the highest rate of relapse of any of the antidepressants.

Reprinted with permission from "Blue Again: Perturbational Effects of Antidepressants suggest Monoaminergic Homeostasis in Major Depression," by P. W. Andrews, S. G. Kornstein, L. J. Halberstadt, C. O. Gardner, & M. C. Neale, 2011, *Frontiers in Psychology, 2,* 159.

homeostatic mechanisms. However, the aberrant neurobiology that underlies the episode is ready to spring back like a coiled spring whenever the ADMs are stopped.

Oppositional tolerance predicts that the more an ADM perturbs the underlying neurotransmitter systems, the greater the likelihood of relapse once it is stopped. That is exactly what is found in discontinuation trials in humans (Andrews et al., 2011). As shown in Fig. 3, depressed patients who remit on placebo (no immediate biological effect) are less likely to relapse following discontinuation than those who remit on SSRIs (affecting serotonin only), followed by the serotonin-norepinephrine reuptake inhibitors (SNRIs affecting both serotonin and norepinephrine) and the TCAs (affecting norepinephrine, serotonin, and acetylcholine), and finally the MAOIs (affecting serotonin, norepinephrine, and dopamine). In essence, the greater the perturbation caused by the specific class of ADM, the greater the risk of relapse following discontinuation.

The question then becomes whether the end of the underlying episode (aka recovery) is delayed as long as a patient stays on medication. That is exactly what would be predicted if ADMs lock down the homeostatic mechanisms that would otherwise have brought about spontaneous remission. There is no reason to presume that the influence of ADMs on those mechanisms will fade so long as the ADMs continue to be taken. In essence, the very mechanisms that suppress symptoms may forestall remission and leave patients at elevated risk for relapse long past the point that the underlying episode would have run its course: the relief brought about by ADMs may represent a "false" remission in name only in which the manifest symptoms are suppressed but the underlying episode continues unabated. If this logic is correct, ADMs may forestall the natural progression to recovery and keep patients at elevated risk of relapse whenever they are stopped.

Recent theoretical reformulations regarding how ADMs actually work focus on changes in social-emotional processing (rapid), as well as the role of neural plasticity downstream in the postsynaptic neuron (slower), but all start at the synapse and all involve "hijacking" the homeostatic mechanisms that regulate the monoamine neurotransmitters (Harmer, Duman, & Cowen, 2017). Thus, all are susceptible to the concern that they prolong the life of the underlying episode.

In a landmark RCT, Kupfer et al. (1992) showed that depressed patients who had recovered and were maintained on imipramine, a TCA, for three years had a risk of recurrence when switched to placebo as high as the risk of recurrence of those who had been continued on ADMs for four months before being switched to placebo. The authors concluded "active imipramine treatment is an effective means of preventing recurrence beyond 3 years and that patients … merit continued prophylaxis for at least 5 years." This and other similar RCTs showing almost universally a high rate of relapse or recurrence following discontinuation of ADMs have led to the clinical saying "with depression, what gets you well, keeps you well." Life-long treatment with an ADM for patients with recurrent depression has become a common practice. The ACNP Task Force was clear that the notion that risk of renewed symptoms was lower for recovered patients (those kept on ADM for the expected duration of the underlying episode) relative to those who had recently remitted (still within the expected life of the underlying episode) was based on an as yet unproven supposition and not necessarily an empirical fact (Rush, Kraemer, et al., 2006). We think these results indicate that ADMs maintain the underlying episode by interfering with the neurobiological processes involved in spontaneous remission: while ADMs may be beneficial in the short-term by suppressing symptoms, they may be iatrogenic in the long run by keeping the underlying episode alive and ready to snap back.

At the beginning of the past decade, Robert Whitaker, an investigative journalist, published a provocative book called *The Anatomy of an Epidemic* in which he asked whether things had gotten better with the advent of the psychiatric medications (Whitaker, 2010). His conclusion was that they decidedly had not. He pointed to skyrocketing rates of psychiatric disability, the emergence of "new" diagnoses like pediatric bipolar disorder, and a coarsening of the disorders with respect to chronicity and recurrence and concluded that, if anything, things have gotten worse. As shown in Table 1, each of those observations can be explained in other ways. But, doing so requires nearly half a dozen different explanations whereas Whitaker requires just one: that ADMs suppress symptoms in the short run at the expense of worsening the course of the underlying disorder. That does not mean that Whitaker is right, but in the history of science, parsimony usually prevails. His hypothesis is in line with national epidemiologic surveys conducted in Australia, Canada, England, and the U.S. that have shown no reduction in the prevalence of depression despite a four-to five-fold increase in the population exposed to ADM during the past 25 years (Jorm et al., 2017).

We do not yet know whether ADMs prolong the duration of the underlying episode, but we do know how that can be tested. That is something that we will return to at the end of the article, but first we want to discuss CBT, how it compares to ADM from an evolutionary

Table 1
Whitaker's iatrogenic medication concerns and possible alternative explanations.

Iatrogenic Medications	Alternative Explanations
Explosion in disability rates	Disability criteria more liberal
Unmedicated patients do better in long run	"Sicker" patients more likely medicated
Prognoses used to be better	Earlier tracking methods less precise
Medications worsen long-term course	Medication withdrawal unmasks disorder
Pediatric bipolar disorder since medication	Always there just misdiagnosed
Single parsimonious explanation	Multiple explanations required
If Whitaker is right:	**If Whitaker is wrong:**
We could be creating/worsening disorders	Patients might stop medications they need

Adapted with permission from "*Anatomy of an epidemic: Magic bullets, psychiatric drugs, and the astonishing rise of mental illness in America,*" R. Whitaker, 2010, New York: Crown Publishers.

("adaptationist") perspective, and what treatment is optimal for whom.

5. How does CBT compare to ADMs?

CBT and ADMs appear to have comparable efficacy in the acute treatment of nonpsychotic unipolar depression (Weitz et al., 2015). Each appears to have a specific effect relative to pill-placebo controls (DeRubeis et al., 2005; Dimidjian et al., 2006), at least among patients with more severe depressions (Driessen, Cuijpers, Hollon, & Dekker, 2010; Fournier et al., 2010), and there are indications that different subsets of those patients with more severe depressions will be differentially responsive to each (DeRubeis et al., 2014). However, there are robust indications that patients treated to remission with ADMs are more than twice as likely to relapse following treatment termination than patients treated to remission with CBT (Cuijpers et al., 2013). Moreover, the two studies that kept remitted patients on continuation ADM for an additional year (long enough to meet criteria for recovery) found that prior exposure to CBT (stopped a year earlier) reduced risk for recurrence relative to prior ADM following discontinuation (Dobson et al., 2008; Hollon et al., 2005). The question then becomes how two such maximally different interventions can be so similar in the magnitude of their acute effects (albeit in different subsets of patients with more severe depression) and yet so dissimilar with respect to whether they are enduring (or possibly iatrogenic).

It's all about the squids and sea bass. We think that the answer may lie with evolutionary biology. If depression is an adaptation that evolved to serve a function, the closer a given intervention comes to resolving the problem that adaptation evolved to serve, the more likely it is to provide a real and lasting benefit. We illustrate this point with a study that examined the role of pain in helping squid avoid being eaten by sea bass (Crook, Dickson, Hanlon, & Walters, 2014). As shown in Fig. 4, sea bass eat squid and squid go through a series of evasive tactics in the presence of a sea bass to avoid being eaten. Crook and colleagues maimed two groups of squid by cutting off a single swimmer; in one group the surgery was performed under anesthesia and in the other it was not. Two other groups of squids underwent no surgery, with one group again administered anesthesia and the other not in a 2x2 factorial. One squid from each of the four groups was then placed in a tank with a sea bass and rates of predation observed. The squids that were not maimed were the least likely to be eaten regardless of whether they had been anesthetized or not. The squids that had been maimed under anesthesia were the most likely to be eaten; they began their evasive tactics no sooner than the squids that had not been maimed but were less efficient swimmers due to their surgeries. Curiously, human observers watching them swim could not detect which squids had been maimed, but the sea bass could. The squids that had been maimed without the benefit of anesthesia were more likely to be eaten than those that had not been maimed but significantly less likely to be eaten than those who had been operated on under anesthesia. The way they managed to do that was by starting their evasive maneuvers earlier than the squids maimed under anesthesia; this the investigators interpreted as an adaptive mechanism (beginning the evasive maneuvers sooner) triggered by the pain (an evolved adaptation that signifies tissue loss).

Treatment implications. If Andrews and Thomson (2009) are correct that depression has evolved to allocate energy to analytical rumination so as to solve complex problems, treatments like CBT that facilitate problem solving might be advantaged over ADMs in the long run. CBT is a skills-based approach that focuses on helping patients identify the source of their distress and generate action plans to resolve those problems. It is a well-established principle in psychotherapy research that those treatments that best capitalize on an individual's strengths tend to work better than those that merely try to compensate for their weaknesses (Lorenzo-Luaces, Peipert, Romero, Rutter, & Rodriguez-Quintana, 2021). If evolution has already prepared the brain to "ruminate to resolution" in the face of complex social problems, then CBT may capitalize on that propensity in a manner that ADMs cannot.

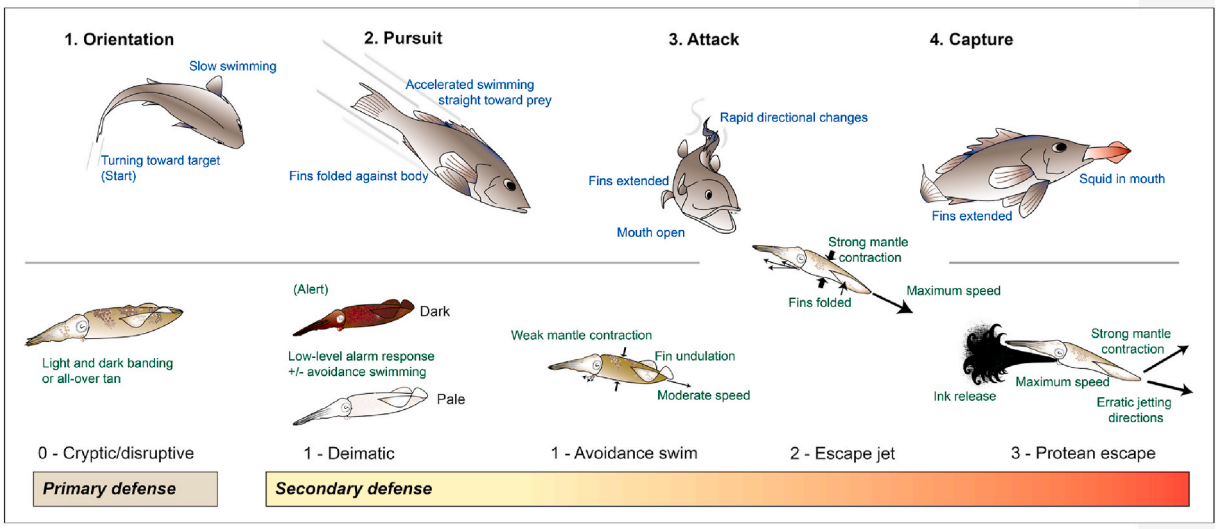

Fig. 4. It's All About the Squids and the Sea Bass (Pain as an Evolved Adaptation): Top: Four stages of predator behavior. ***Orientation*** is the first change in direction toward a squid from an ongoing swimming trajectory and the distance from fish to squid is the "start-distance'' of the predation attempt. ***Pursuit*** is an accelerated, direct approach toward a squid, with the fish's dorsal, pectoral, and caudal fins folded. ***Attack*** is close proximity "grappling,'' with the fish's mouth open and fins extended to facilitate rapid directional changes. ***Capture*** is any part of the squid's body caught in the mouth of the fish. **Bottom:** defensive responses of squid to the fish. ***Primary defense*** (avoiding detection via crypsis) escalates to secondary defenses once the squid is alerted. Crypsis - chromatophore patterns of disruptive banding while sitting on the substrate or all-over beige when swimming - occurs in the absence of encounters and often during early encounter stages; it received an escalation score of 0. Distance between squid and fish at the first secondary defensive behavior is the "alert distance.'' ***Secondary defenses*** were scored based on their typical progression. Deimatic chromatophore displays that distract or startle a predator were scored 1, as were slow avoidance swimming evoked by distant threat. Escape jetting without inking was scored 2. This typically followed expression of behaviors scored 1. Ink release, which was almost always combined with erratic escape jetting, was scored 3. The highest escalation score was recorded for each predatory encounter.
Adapted with permission from "Nociceptive sensitization reduces predation risk," by R. J. Crook, K. Dickson, R. T. Hanlon, & E. T. Walters, 2014, *Current Biology, 24,* p. 1122.

That being said, there are different types of CBTs, some that explicitly target cognition and some that do not. Cognitive therapy has been the most extensively studied type of CBT and is the easiest to fit into this narrative. Cognitive therapy is based on the premise that inaccurate beliefs and maladaptive behaviors drive distress (Beck, Rush, Shaw, & Emery, 1979). Cognitive therapy encourages patients to engage in an analytical process to examine those beliefs and to use their own behaviors to test their accuracy. The emphasis is not just on relieving distress but also on learning how to accurately identify its causes and to come up with an action plan to bring about its resolution. We think that cognitive therapy works by facilitating the functions that depression evolved to serve, whereas ADMs only relieve the distress. In effect, we think that CBT works (and has its enduring effect) as a function of helping patients "ruminate" in a more efficient fashion that helps to structure the questions that they ask about the causes of their distress and the search for solutions to their problems (Hollon & Garber, 1990).

Some patients do get "stuck" and when they do it is usually because they have adopted a stable trait theory ("I am unlovable" or "I am incompetent") to account for their distress. In such instances, the classic first move in CBT is to encourage them to consider a more behaviorally based explanation ("I chose the wrong strategies") and collect information and run behavioral experiments to test between them (Hollon, DeRubeis, Andrews, & Thomson, 2020). At risk of stretching our metaphor, we think that ADMs may "anesthetize" the patient but leave them no further along in dealing with their problems, whereas cognitive therapy may move the problem resolution along in a manner that depression evolved to address.

It is also the case that CBT appears to have an enduring effect that reduces risk for both relapse (Cuijpers et al., 2013) and recurrence (Dobson et al., 2008; Hollon et al., 2005). Precisely how it does so is still unknown, but it likely involves some sequential progression from the acquisition of purely compensatory skills (compensation) to an actual change (accommodation) in the underlying diatheses (causal schema) that had put those who are recurrence prone at elevated risk (Barber & DeRubeis, 1989). Strunk, DeRubeis, Chiu, and Alvarez (2007) have shown that those patients who best incorporate the compensatory skills taught in CBT are least likely to relapse following the end of treatment. They also are less likely to generate negative self-referential trait ascriptions and more likely to generate pragmatic solutions when presented with hypothetical problems to solve than those patients who are at greater risk of relapse. Our clinical experience suggests that these processes unfold in a sequential fashion; patients first acquire the compensatory skills but have to remember to apply them in problematic situations. Over time, the application of these skills becomes second nature (habitual) and, as it does, the underlying depressotypic schema itself starts to change (accommodates).

Mindfulness based cognitive therapy (MBCT) is something of an anomaly since it ostensibly works by helping patients disengage from the ruminative process (Segal, Williams, & Teasdale, 2012). While it does appear to have a prophylactic effect for patients with history of three or more prior episodes (likely the recurrence prone) and especially those with a history of childhood trauma (Williams et al., 2014), it is not all that effective in preventing relapses preceded by recent life events and especially among those patients in their first or second episode (mostly the depression possible) (Ma & Teasdale, 2004). Moreover, it is little used for the treatment of patients who are acutely depressed (Kuyken et al., 2016). This is exactly the pattern that would have been expected if depression were an adaptation that evolved to help resolve complex problems that were current and not rooted in the distant past.

Does behavioral activation fit the template? Behavioral activation (BA), the best-established of the behavioral interventions, does not address cognition directly but does focus on helping patients develop action plans to deal with their life problems (Martell, Addis, & Jacobson, 2001). This is exactly the end-state that the analytical rumination process is presumed to achieve. If the goal of analytical rumination is to arrive at a solution to whatever complex interpersonal problem first triggered the distress, then any intervention that facilitates implementing that solution should facilitate the function that analytical rumination evolved to serve. BA does provide a rationale (a deficit in rewards that snowballs on itself often triggered by avoidance) and strategies for devising action plans. In essence, BA likely helps patients to deal more effectively with the problems they face in a manner that bypasses cognition entirely.

Does adding ADM undercut CBT's enduring effect? There is reason to think that adding ADM may undercut CBT's enduring effect. Although CBT's enduring effect is relatively robust when provided alone (seven of eight successes for prior cognitive therapy in Cuijpers et al., 2013, and one for one for prior BA in Dobson et al., 2008), a recent trial found virtually no evidence for an enduring effect when cognitive therapy was provided in combination with ADM (DeRubeis et al., 2020). The absence of a cognitive therapy alone condition precludes drawing any firm conclusions in that regard, but adding ADM did appear to interfere with a cognitive therapy's enduring effect relative to cognitive therapy alone in an earlier trial (Simons, Murphy, Levine, & Wetzel, 1986). Moreover, Barlow, Gorman, Shear, and Woods (2000) observed something similar in the treatment of panic disorder in which CBT alone or in combination with a pill-placebo cut the rates of relapse in half relative to ADM alone or CBT combined with active ADM. This suggests that adding ADM in combination interferes with CBT's enduring effect and that the mechanism is pharmacological in nature. What is needed is a design in which depressed patients are randomized to CBT versus ADM each alone and in combination, treated to remission, and then treatment is withdrawn. If ADMs interfere with CBT's enduring effect, relapse rates for prior combined treatment should be no better than for prior ADM alone and worse than relapse rates with CBT alone. This too can be tested.

It should be noted that if adding ADMs interferes with any enduring effect that CBT may possess, this does not appear to apply to sequential administration. CBT appears to have an enduring effect if it is added after patients are brought to remission with ADM and even appears to facilitate their discontinuation (Breedvelt et al., 2020; Guidi & Fava, 2021). This is consistent with the findings by Barlow and colleagues cited above that having the actual pharmacological agent in the system (rather than merely believing that one was on an ADM) interferes with CBT's enduring effect.

Is CBT's enduring effect an artifact of a selection bias? Designs that follow only patients who remit in treatment are at risk of being biased against prior ADMs due to "differential mortality" on the assumption that high-risk patients are differentially likely to complete and remit or recover on ADM whereas low risk patients will be differentially likely to complete and remit or recover on CBT (Klein, 1996). Only about half the patients initially randomized to treatment complete and remit in any acute trial of either CBT or ADM so as to be eligible to enter the subsequent follow-up. It is quite possible that selection bias has been introduced via subtraction (differential mortality), and that we are left comparing high risk "apples" to low risk "oranges". An earlier test of moderation found that patients with depressions superimposed on personality disorders were more likely to remit on ADM than to CBT and more likely to relapse once ADM was discontinued (Fournier et al., 2008). This is exactly the kind of scenario that could produce a bias against prior ADM. None of the other trials that demonstrated an enduring effect for prior CBT assessed for personality disorder. Thus, it is possible that the superior enduring effect of CBT is an artifact of differential mortality.

6. Are antidepressant medications iatrogenic or is CBT enduring?

We now return to our primary questions: Are ADMs iatrogenic (in terms of prolonging the underlying episode) or is CBT enduring? Given the issues previously described there is a reasonable possibility that ADMs not only interfere with CBT's enduring effect but also have an

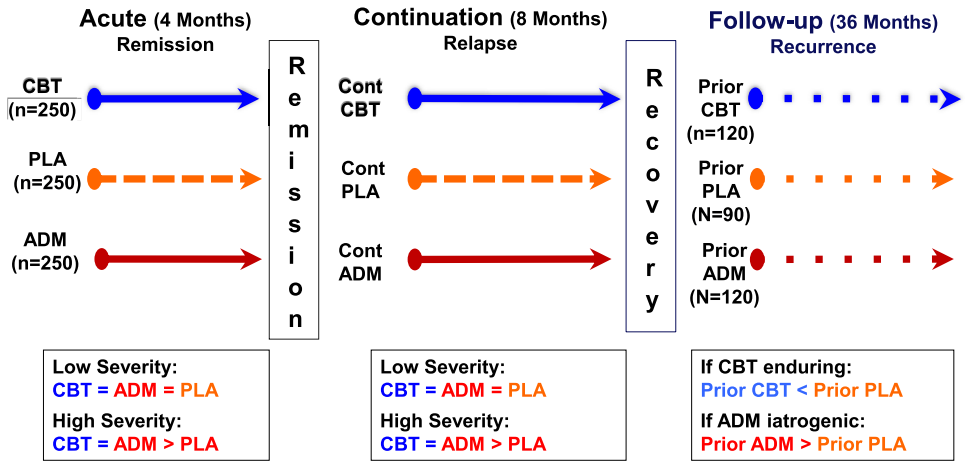

Fig. 5. Does CBT Have an Enduring Effect or is Antidepressant Medication Iatrogenic? If cognitive behavior therapy (CBT) has an enduring effect then patients treated to recovery in that modality will be less likely to experience a recurrence following treatment termination than patients who recover spontaneously on pill-placebo (PLA). If antidepressant medication (ADM) has an iatrogenic effect that prolongs the duration of the underlying episode then patients treated to recovery on that modality will be more likely to experience a recurrence following treatment termination than patients who recover spontaneously on pill-placebo (PLA). Since more high-risk patients are likely to recover in either CBT or ADM, reverse propensity analysis can be used to identify the subset of patients in each most similar to those patients who recover in PLA.
Adapted with permission from "Recent Developments in the Treatment of Depression," by S. D. Hollon, Z. D. Cohen, D. R. Singla, & P. W. Andrews, 2019, *Behavior Therapy, 50(2),* p. 266.

iatrogenic effect of their own that prolongs the length of the underlying episode. We do not know if either is true, but we do know how to resolve the questions. Fig. 5 presents the kind of design that could be used to determine whether ADMs are iatrogenic or CBT enduring. In that design, depressed patients randomized to CBT or ADM or pill-placebo (PLA) would be treated to "recovery". (We put the term "recovery" in quotes since the basic premise being tested is that ADMs suppress symptoms in a manner that prevents the underlying episode from running its course. If so, then what appears to be "recovery" among ADM patients is actually "sustained remission" and not true "recovery".) Patients would then discontinue their treatment and be followed treatment-free for at least 6–12 months to assess for recurrence. If CBT truly has an enduring effect (something more than just an artifact of differential mortality), then patients who recover in CBT should be less likely to experience a recurrence than patients who recover on PLA. If ADMs have an iatrogenic effect, then patients who "recover" on ADM should be more likely to recur than patients who recover on PLA. PLA is the nonspecific control that has long been needed to determine whether CBT is enduring or ADM iatrogenic (or both). We should note that "sustained recovery" (staying in treatment long enough to first remit and then recover and then stay free from recurrence across the subsequent follow-up) is the more pragmatic outcome for a design like this (DeRubeis et al., 2020). However, recurrence following recovery is the primary outcome of theoretical interest in this trial because one of the two questions is whether ADMs prolong the underlying episode by virtue of locking down the homeostatic mechanisms that would otherwise bring the episode to an end.

If this trial also had a group randomized to both CBT and ADM, it could determine whether ADM prevents the enduring effect of CBT: patients who "recover" in that modality should have a rate of recurrence similar to those who "recover" on ADM alone and higher than in those who recover on CBT alone. There are two reasons for not including such a combined condition in the three-armed trial depicted in the Figure: 1) adding an additional arm is costly in terms of both number of participants and price (inflating each by about a third); and 2) it is not necessary to treat patients to recovery (the longer and more expensive outcome) to test for interference; remission alone would do. To determine whether ADMs have an iatrogenic effect that prolongs the life of the underlying episode it is necessary to treat patients to the point of what should be recovery since the concern is that medications lock in place the homeostatic mechanisms that otherwise would bring the episode to an end. However, to determine whether adding ADM interferes with any enduring effect that CBT might have only requires treating patients to remission since differential rates of relapse would be sufficient.

Ethical considerations. The design depicted in Fig. 5 raises obvious ethical concerns about randomizing patients to a presumably less efficacious PLA condition, as well as scientific concerns regarding differential mortality (the risk that the trial will be biased against the active interventions if these interventions get more high-risk patients into recovery). However, these issues can be addressed. Neither CBT nor ADM separates from PLA among patients with less severe depressions (Driessen et al., 2010; Fournier et al., 2010) and the efficacy of each has been inflated by about a third by publication bias (Driessen, Hollon, Bockting, Cuijpers, & Turner, 2015; Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008). The upshot is that neither is as specifically efficacious as is commonly believed. We can estimate that approximately three-quarters of the patients who recover either with CBT or on ADM also will recover on PLA (patients with less severe depression should do as well on PLA as with either CBT or ADM, and the same should be true for about half of the patients with more severe depression). More severe patients are more likely to respond specifically to either ADM or CBT. This can be addressed by monitoring all patients closely across the course of treatment. Patients who do not show a reasonable rate of response can be designated as not remitted or not recovered, withdrawn from their randomized treatment condition, and provided with treatment of a different kind (as in Weissman et al., 1979).

Not doing the kind of trial we are proposing raises even larger ethical questions. CBT is one of the most widely recommended (and practiced) psychotherapies, largely on the strength of its presumed enduring effect (see for example Clark, 2018). ADMs are the third most widely prescribed medication class, with the bulk of those prescriptions written for the SSRIs, largely because they are seen as being relatively safe and efficacious (Pratt et al., 2017). If CBT does not in fact have an enduring effect or if ADMs are iatrogenic, then that is something that the field and the public at large should know. The first principle in any study is to protect the welfare of the participants involved, but, once that is done, the next is to generate information for the benefit of the larger public. Given the stakes involved and the questions raised about the treatments of depression, we believe it would be unethical not to do such a trial.

Scientific considerations. If differential mortality is a threat to the interpretability of comparisons between prior CBT versus prior ADM it is

even more so to comparisons to prior PLA. Both active treatments can be expected to bring more patients to recovery than PLA and it is likely that those additional patients will be at higher risk so as to bias any comparison among recovered patients in favor of prior PLA. The design depicted in Fig. 5 can control for differential mortality if a reverse propensity analysis is used to identify those patients who recover with either CBT or ADM who best match the patients who recover on PLA. It is likely that the excess patients who recover with either CBT or ADM will be different from one another (DeRubeis et al., 2014) but patients who recover on PLA should be as likely to recover with either CBT or ADM. Machine learning can be used to generate selection algorithms (logically equivalent to propensity analyses) that use baseline characteristics to identify those patients in each of the active conditions who best match the smaller number of patients who recover on PLA. We can then restrict our primary tests of differential recurrence to just those patients (see Coffman, Martell, Dimidjian, Gallop, & Hollon, 2007, for an example).

What works best for whom? The reverse propensity analyses described above is a simple variation on the kind of selection algorithm that can be used to identify the optimal intervention for a given patient (Cohen & DeRubeis, 2018). Not only can we use that logic to identify the subset of patients who recover with CBT or ADM that are most like those who recover on PLA to address the issue of differential mortality, we also can generate precision treatment rules (PTRs) in the larger data set to determine which intervention is best for each individual patient. In an earlier placebo-controlled trial restricted to patients with severe depressions (DeRubeis et al., 2005), about 30% of the patients would have done better with CBT than on ADM and a different 30% would have done better on ADM than with CBT; the remaining 40% showed minimal evidence of a differential response and likely would have done as well (or as poorly) on PLA (DeRubeis et al., 2014). Had the optimal treatment been given to each patient, it would have enhanced overall outcome by the magnitude of the drug-placebo difference across the whole sample ($d = 0.30$) and twice that among the patients for whom there clearly was an optimal treatment ($d = 0.60$). We can generate the same kinds of PTRs in our full sample (not restricted to the subset of patients who recover on PLA) to indicate for each patient whether s/he is more likely to recover with CBT or ADM or as likely to recover on PLA.

A recent meta-analysis of the depression treatment literature indicated that active psychotherapies had 9% greater heterogeneity of treatment effects (HTEs) than control conditions, which corresponds to about a standard deviation on a typical depression scale (Kaiser et al., 2020). What this means is that different patients are likely to respond to different active treatments and as noted above the same appears to be true relative to comparisons to ADM (DeRubeis et al., 2014). To the extent that is true, we should be able to make the treatment process more efficient by identifying the optimal treatment for a given patient in advance of entering treatment, rather than relying on trial and error.

That being said, if CBT does prove to have an enduring effect, then it would be preferred for all patients except for those who need to be on ADM in order to recover, and those latter patients are the very ones most likely to need to be maintained on ADM indefinitely. If ADM has an iatrogenic effect that suppresses symptoms at the expense of keeping patients at elevated risk for relapse, then any "tie score" with respect to "recovery" for a given patient would favor CBT over ADM over the longer-term.

Moderated mediation. Finally, we can test the analytical rumination hypothesis by monitoring patterns of rumination across the trial. The analytical rumination questionnaire (ARQ) has separate subscales for measuring causal analysis and problem solving (Barbic, Durisko, & Andrews, 2014). The analytical rumination hypothesis posits a clear sequential causal model over time that received initial confirmation in a longitudinal observational study with hospitalized patients (Sevcikova et al., 2020). As described above, in this model, increases in depression drive increases in causal analysis; causal analysis then facilitates the process of generating effective solutions, which in turn decreases depression (a closed system in engineering terms). If the analytical rumination hypothesis is correct, this is the process that should underlie spontaneous remission among patients on PLA. That process should be accelerated among patients treated with CBT (if truly prophylactic) and suppressed among patients treated with ADM (if truly iatrogenic). Thus, the design proposed not only can resolve the questions as to whether CBT truly is enduring or ADM truly iatrogenic, it also can test (and possibly disconfirm) the analytical rumination hypothesis with respect to how those changes come about.

7. Conclusions

The analytical rumination hypothesis suggests that depression is an adaptation that evolved to serve a purpose in our ancestral past and may still be doing so today. It further suggests that depression evolved to keep people focused on the source of their distress until they could come up with a solution to resolve the relevant problem. CBT appears to enhance this adaptive process and to have an enduring effect not found for ADM. The apparent enduring effect of CBT that protects against subsequent relapse and recurrence might be an artifact of a selection bias ("differential mortality") whereas concerns have been raised that ADMs suppress acute distress at the expense of prolonging the underlying episode. A study design has been proposed in which patients treated to recovery with CBT or ADM are compared to a true "no specific mechanism" control condition (i.e., an inert pill-placebo). If CBT is truly enduring, then patients who recover in CBT should do better than controls once treatment is terminated. If ADM is truly iatrogenic, then patients who recover on ADM should do worse. We know that prior CBT outperforms prior ADM, but we do not yet know why. We hypothesize that CBT facilitates the processes that depression evolved to serve, whereas ADM only suppresses the acute distress that those processes generate. We do not know if either or both are true, but we do know how to test them. The proposed study will answer these questions and deserves to be done.

Declaration of competing interest

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