American Psychologist

© 2020 American Psychological Association
ISSN: 0003-066X

2020, Vol. 75, No. 9, 1207–1218
http://dx.doi.org/10.1037/amp0000728

Is Cognitive Therapy Enduring or Antidepressant Medications Iatrogenic? Depression as an Evolved Adaptation

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Patients treated to remission with cognitive therapy are less than half as likely to relapse following treatment termination as patients treated to remission with antidepressant medications. What remains unclear is whether cognitive therapy truly is enduring or antidepressant medications iatrogenic in terms of prolonging the life of the underlying episode. Depression is an inherently temporal phenomenon and most episodes will remit spontaneously even in the absence of treatment. There is reason to believe that depression is an adaptation that evolved because it keeps organisms focused on (ruminating about) complex social issues until they can be resolved and that medications work not so much by addressing a nonexistent deficit in neurotransmitters in the synapse as by perturbing underlying regulatory mechanisms to the point that they reassert homeostatic control over those systems. If the latter is true then medications may work to suppress symptoms in a manner that leaves the underlying episode unaddressed and patients at elevated risk of relapse whenever they are taken away. Cognitive therapy is predicated on the notion that people become depressed because they misinterpret life events in a negative fashion and that helping them examine the accuracy of their beliefs will relieve their distress. Such an approach would not work if patients were not capable of thinking clearly (if their "brains were broken") and it is likely that cognitive therapy works by making rumination more efficient so as to facilitate the resolution of the complex social issue(s) that brought the episode about.

Public Significance Statement
There is reason to think that depression may be an adaptation (like pain or anxiety) that evolved in our ancestral past to help resolve complex social problems. If true then interventions like cognitive therapy that facilitate the functions that depression evolved to serve may be preferred over antidepressant medications that merely anesthetize the distress.

Keywords: depression, cognitive therapy, antidepressant medications, evolved adaptation

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Depression is an inherently temporal phenomenon. Any given episode tends to remit spontaneously even in the absence of treatment but recurrence is common (at least among people seeking treatment). There is reason to believe that depression may be an evolved adaptation (like pain or anxiety) that increases reproductive fitness (the likelihood that one's gene line will pass on). If so, then any treatment that facilitates the functions that depression evolved to serve is likely to be preferred to one that only anesthetizes the distress. This article begins by illustrating the adaptive role that pain plays in helping squid avoid predation by sea bass and then goes on to discuss the possible adaptive role that depression plays in resolving complex social issues. It next considers whether cognitive therapy truly is enduring (existing indications might be an artifact of differential mortality) or if antidepressant medications (ADMs) are iatrogenic (as evolutionary theory might suggest). Differences in risk are clear but not their source or their implications.

Editor's note. Steven D. Hollon received the 2020 APA Award for Distinguished Scientific Applications to Psychology. In association with the award, Hollon was invited to submit a manuscript to *American Psychologist*, which was peer reviewed. The article is published as part of the journal's annual Awards Issue.

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This research was supported in part by grants from the National Institute of Mental Health MH33209 (R01), MH55875 (R10), MH60713 (R01), and MH01697 (K02).

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The article ends by describing the kind of study that would be needed to resolve both questions.

Is Depression an Evolved Adaptation?

All organisms engage in common survival strategies in that they approach stimuli that are useful and avoid those that might cause harm (LeDoux, 2019). Precisely what tactical form those survival strategies take varies across species but all were shaped by natural selection. Any organism must do two things in the course of its daily activity; it must get lunch and it must avoid becoming someone else's lunch. Neural systems have evolved to both pursue appetitive stimuli (the behavioral activation system) and to avoid potential threat (the behavioral inhibition system; Gray, 1990). The pursuit of appetitive stimuli is associated with positive affect, whereas the avoidance of aversive stimuli is associated with negative affect or pain.

Evolutionary theorists disagree as to whether those affects play a causal role in motivating the specific survival response (Panksepp, 1998) or are merely its consciously experienced byproduct (LeDoux, 2019). However, all would agree that the survival behaviors associated with affective experiences were selected for in our ancestral past because they coordinated differentiated "whole body responses" to different type of opportunities or threats. Different affects motivate (Panksepp, 1998) or are associated with (LeDoux, 2019) different types of behaviors that the body is then readied physiologically to support. Pain helps prevent additional tissue damage and anxiety helps to avoid imminent risk. Different affects are associated with these different instantiations but in each the body is readied for its maximally effective response to a given opportunity or challenge (see Snedden, Elwood, Adamo, & Leach, 2014, on pain and Tooby & Cosmides, 1990, on affect).

The Squids and the Sea Bass

This point can be illustrated by an elegant study by Crook, Dickson, Hanlon, and Walters (2014). Sea bass eat squid and squid appear to prefer not to be eaten. When a sea bass becomes aware of a squid it starts a series of orienting behaviors culminating in an attack and (if lucky) a meal. When squid become aware of the presence of a sea bass they start to engage in a series of defensive maneuvers evolved to reduce the risk of predation. What Crook and colleagues did was to maim the squid by cutting off one of their swimmers in a 2×2 experimental design; squid were either maimed or not maimed either under anesthesia or not. Then one squid from each of the four experimental conditions was placed in a tank with a sea bass and rates of predation observed. The surgeries were performed six hours before the test of predation, more than enough time for the effects of the anesthesia to wear off. Human observers could not tell which squid had been maimed from the way it swam, but the sea bass could (that is the kind of thing that predators do for a living). Those squid that had not been maimed had the lowest rates of predation (as expected) but those squid that had been maimed under anesthesia were more likely to be eaten than those that had been maimed without. The reason was that the pained squid began their evasive maneuvers sooner whereas the squid that had been maimed under anesthesia started no sooner than the intact squid. The moral of the story is that the pain served an adaptive purpose and alerted the injured squid to start evading sooner.

Depression as an Evolved Adaptation

There is reason to think that depression also is an evolved adaptation like pain or anxiety. There are several different evolutionary explanations for depression and any or all might hold, but the one most relevant to the current thesis for reasons both anatomical and neurochemical is the analytical rumination hypothesis (ARH) proposed by Andrews and Thomson (2009). According to the ARH, depression typically is triggered by complex social problems that affected fitness in our ancestral past. Humans evolved in small family groups and exclusion from the troop would have been a virtual death sentence (the excluded individual would have been picked off by predators or starved to death) particularly for females caring for an infant. Unipolar depression is twice as common in women as in men and this gender disparity starts in early adolescence when females become capable of reproduction (Hankin & Abramson, 2001). That is an unusual life course for a "disease" to follow (most kill you in your infancy or in your dotage); that alone would lead an evolutionary biologist to suspect that depression is an evolved adaptation. The reason that the ARH is the most compelling of the evolutionary theories of depression is that it provides an explanation for the way that metabolic resources get distributed in the body and especially the brain when somebody gets depressed.

Evolutionary biologists engage in a process called reverse engineering when trying to understand the function of an adaptation. Ancestral selection pressures gave rise to the adaptation so studying its structure and operation likely reveals something about the functions that it evolved to serve (Andrews, Gangestad, & Matthews, 2002). There are multiple depression-like syndromes that each involves low mood, lassitude, and loss of interest in hedonic pursuits (Andrews, Bharwani, Lee, Fox, & Thomson, 2015). When a person is dealing with an infection, metabolic resources are directed away from growth and hedonic pursuits and toward the immune system. When a person is starving metabolic resources are directed away from immune functions and hedonic pursuits and toward maintenance of vital body organs and increased motor activity (foraging). In neither

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case does the individual start to ruminate (unless it is about food in the case of starvation), if anything, people with infections or in the process of starving report a slowing down of cognition. When someone has a clinical depression (and especially one with melancholic features), metabolic resources are directed away from hedonic pursuits (with the consequence that pleasures are not pursued and behaviors decrease) and toward the cortex where it makes the individual resistant to distraction and inclined to dwell on (ruminate about) current concerns related to their distress. These different responses did not evolve by accident; natural selection favored each because they increased the likelihood of passing on one's gene line (not just one's genes) in response to different environmental challenges (Hamilton, 1964).

It is especially interesting that serotonin (the primary biogenic amine targeted by most ADMs) is the neurotransmitter that plays the key role in energy transfer throughout the body and especially the brain (Andrews et al., 2015). Serotonin coevolved with mitochondria, once free-living endosymbiotic organelles that generate most of the chemical energy that fuels the cell's biochemical reactions (Picard, McEwen, Epel, & Sandi, 2018). Serotonin (like the other biogenic amines dopamine and norepinephrine) is a very ancient neurotransmitter with cell bodies buried deep in the brain stem (it has been around a long time in evolutionary terms) and plays a key role in mitochondrial biogenesis (Fanibunda et al., 2019).

What this suggests is that depression evolved to facilitate rumination. This is anathema to clinicians (the author included) who tend to view rumination as at best a symptomatic consequence of depression and at worst something that prolongs the disorder (Nolen-Hoeksema, 2012). It is clinicians who have given rumination a bad reputation, largely because it is seen as a potential cause of distress. But rumination can involve the "deep and considered thought about something" and is not necessarily a repetitive regurgitation of the same material in an endless loop; its dictionary definition is to "go over in the mind repeatedly and often casually or slowly . . . to engage in contemplation" (Merriam-Webster's New Collegiate Dictionary, 2014). Humans have two information processing styles, one fast and intuitive (Type I) and the other slow and attentionally demanding (Type II; Evans & Stanovich, 2013). Type II is energetically expensive (it requires working memory) so it is more likely to be employed when there are complex problems to be solved that Type I thinking cannot resolve. This is what happens in depression.

According to the ARH, rumination involves two sequential processes, causal analysis (to identify the source of the problem) and problem solving (to come up with a plan to do something about it) and this more complex information processing is facilitated by the more powerful Type II thinking. A recent cross-sectional study that assessed both was consistent with this model; depression was positively correlated with causal analysis and causal analysis was positively correlated with problem solving, but problem solving was negative correlated with depression (Bartoskova et al., 2018). It remains to be seen whether depressed patients actually go through a sequential process, but any theory of depression must account not only for why it begins but also why it goes away. In engineering terms, the ARH is a closed system (one that returns to baseline) that could provide an account of how spontaneous remission came about in ancestral times.

To the extent that this is true then any intervention that facilitates the functions that depression evolved to serve is likely to work better in the long run than one that simply anesthetizes the pain. This suggests is that those interventions that facilitate the resolution of complex social problems might do a better job than ADMs, especially if they have enduring effects (cognitive therapy) or teach interpersonal skills (interpersonal psychotherapy).

Treatment of Depression by Psychotherapy and Medications

Depression is an eminently treatable disorder and there are several different types of psychosocial interventions that are all comparably efficacious (American Psychological Association, 2019). Cognitive therapy was the first psychosocial interventions to hold its own versus ADM in the treatment of depression and it remains the most extensively tested. It also appears to have an enduring effect that medications simply lack (Hollon, Stewart, & Strunk, 2006). It is likely that other psychosocial interventions have enduring effects as well, although such an effect has been found only in one-off trials for behavioral activation (Dobson et al., 2008) and long-term psychoanalytic psychotherapy (Fonagy et al., 2015); replication is needed.

The evidence for cognitive therapy's enduring effect is remarkably robust (seven out of eight relevant trials show such an effect) and large in magnitude (it cuts risk for relapse after treatment termination by more than half relative to prior ADM; Cuijpers et al., 2013). Like the ARH, it also focuses on cognition. Cognitive therapy is predicated on the notion that negative beliefs and maladaptive information processing contribute to the onset and maintenance of depression and that helping to correct those errors in thinking (usually by encouraging the patient to use his or her own behaviors to test their validity and the use of Socratic questioning to examine their evidential base) can relieve that distress. Patients are taught to consider alternative explanations for the problems that they face (most enter treatment with the notion that they are defective in some way), to consider the evidence for and against those various hypotheses, and to parse real from imagined implications. In essence, patients are taught strategies for examining the causes of their problems and coming up with possible solutions. This provides a striking parallel to the move from causal analysis to

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problem solving posited by the ARH and in many respects can be seen as making the rumination more efficient (Hollon & Garber, 1990).

Is Cognitive Therapy's Enduring Effect an Artifact of Differential Mortality?

The evidence for cognitive therapy's enduring effect may be robust, but recent indications have emerged that suggest that it might have be an artifact of differential mortality (Klein, 1996). In the typical trial, only about 60% of the patients initially randomized both complete treatment and respond to a sufficient extent that treatment can be stopped and relapse monitored across a subsequent naturalistic follow-up. Although patients are randomized at the outset, differential mortality (either attrition or nonresponse) could undermine the integrity of that initial randomization if different kinds of patients "survive" to enter the naturalistic follow-ups from the different conditions. It is not enough for response rates to be similar, the same kinds of patients must both complete and respond from each condition or differential mortality can bias the follow-up.

In an earlier comparison that found cognitive therapy to be as efficacious as ADM and each superior to pill-placebo among patients with more severe depressions (DeRubeis et al., 2005), patients without Axis II disorders (roughly half the sample randomized) were about 20% more likely to respond to cognitive therapy than to ADM whereas patients with Axis II disorders (the other half of the sample initially randomized) showed the opposite pattern to the same extent (Fournier et al., 2008). In that trial, it was the patients with Axis II disorders who were most likely to relapse after medications were taken away (patients without Axis II disorders were no more likely to relapse if withdrawn than if continued). If Axis II patients are more likely to respond to ADM than to cognitive therapy and more likely to relapse when ADM is taken away, then differential mortality (who makes it into continuation) could account for cognitive therapy's apparent enduring effect. None of the other studies that found an "enduring effect" for cognitive therapy assessed for Axis II, so differential mortality remains a viable alternative explanation.

Does ADM Interfere With Cognitive Therapy's Enduring Effect?

An even more recent trial raises the concern that adding ADM in the form of combined treatment (Hollon et al., 2014) may interfere with cognitive therapy's enduring effect (DeRubeis et al., 2020). In that trial, $N = 452$ patients with major depression but transdiagnostic with respect to other nonpsychotic Axis I and Axis II disorders and comorbid medical conditions were randomized to ADM alone or ADM plus cognitive therapy. Patients were treated first to remission (four weeks of minimal symptoms) and then to recovery (six months without relapse). Treatment could last up to 42 months and patients who relapsed during continuation were brought back to remission and started on a "new clock" to see if they could meet criteria for recovery. Prescribing clinicians were free to prescribe whatever medications were needed to bring about recovery and cognitive therapists were free to continue treatment into the continuation phase for patients at elevated risk.

What was found was that adding cognitive therapy to ADM enhanced rates of recovery by about 10% across the full sample. However, this effect was heavily moderated such that it only applied to the third of the sample that was nonchronic but more severe (who showed a 30% increment) but not to the third of the sample that was chronic (they did not benefit from adding cognitive therapy) or the third of the sample that was nonchronic but less severe (they did not need cognitive therapy to be added; Hollon et al., 2014). However, there was not even a hint of an enduring effect for prior exposure to cognitive therapy (DeRubeis et al., 2020). This despite the fact that such an effect had been found in an earlier trial restricted to patients with severe depression that was conducted in two of the same three study sites using many of the same therapists (Hollon et al., 2005). The failure to replicate was striking and demands an explanation.

This raises the concern that adding ADM in combination may interfere with any enduring effect that cognitive therapy may have. That is what happened in an even earlier trial comparing cognitive–behavioral therapy (CBT) to ADM alone and in combination in the treatment of panic disorder (Barlow, Gorman, Shear, & Woods, 2000). Patients treated to remission with CBT alone were half as likely to relapse following treatment termination as patient treated to remission with ADM. Combined CBT plus ADM was little more than expensive pharmacotherapy; patients treated to remission in that condition were as likely to relapse as patients treated to remission with ADM alone. Patients treated to remission with the combination of CBT plus pill-placebo did not show this suppressive effect; they were no more likely to relapse than patients treated with CBT alone. What this suggests is that whatever was going on in the Barlow study, the underlying causal mechanism was purely pharmacological and not psychological in nature.

Does ADM Have An Iatrogenic Effect That Prolongs the Underlying Episode?

The larger question is whether ADM has an iatrogenic effect that prolongs the life of the underlying episode. Figure 1 represents the "5 Rs" of depression (Kupfer, 1991) an immensely influential conceptual model that has guided psychiatric practice for over for a quarter of a century (Frank et al., 1991; Rush et al., 2006). Response is defined as better but not fully well, whereas remission is defined as the full normalization of symptoms and is distinguished from recovery by which point the underlying episode has

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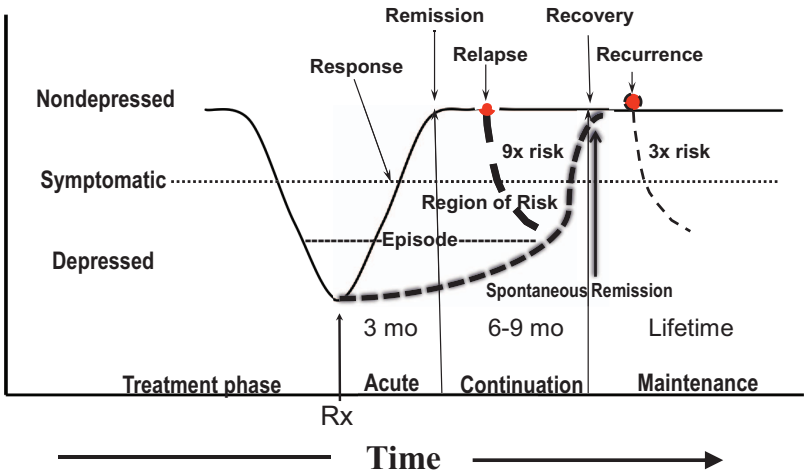

Figure 1. The 5 "Rs" of depression: This figure served as the inspiration for the consensus definitions developed by the MacArthur Network chaired by David Kupfer and published (sans figure) by Frank et al., 1991 in the Archives of General Psychiatry. Response refers to better (typically a 50% reduction 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 wholly new episode. The risk for relapse (before the underlying episode has run its course) is considered 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 initial remission. After that point in patients can (perhaps) be brought off medications but patients with a history of chronic or recurrent depression (85% of the patients in clinical settings) are increasingly being kept on medications for the rest of their lives. Adapted with permission from "The Long-Term Treatment of Depression," by D. J. Kupfer, 1991, *Journal of Clinical Psychiatry, 52*(Suppl 5), 28–34. See the online article for the color version of this figure.

run its course. Relapse refers to the reemergence of symptoms during the life of the treated episode and recurrence refers to the onset of a wholly new episode following recovery.

It has been standard practice in psychiatry for at least the last quarter century to keep patients on medications for six months to a year following initial remission so as to forestall relapse (Frank et al., 1991; Rush et al., 2006). Implicit in this recommendation is the notion that the underlying episode lives on even as its manifest symptoms are being suppressed. The ACNP Task Force report describes it thus:

> Consequently, the distinction between remission and recovery depends on the interval following symptom reduction that reflects the resolution of the *underlying neurobiology* (italics added) of the MDE. . . . 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 et al., 2006, p. 1843)

What this implies is that while ADMs suppress manifest symptom expression, they do not address the neurobiology driving the underlying episode; that is, they are purely palliative and not curative (Seligman, 1994). It also implies that ADMs can suppress symptoms without affecting the underlying neurobiology. In fact, synaptic serotonin and norepinephrine are under homeostatic control and the brain alters its synaptic parameters in response to taking ADMs (Andrews, Kornstein, Halberstadt, Gardner, & Neale, 2011). It is illogical to assume that ADM can suppress symptoms "passively" without affecting underlying homeostatic mechanisms and potentially problematic to assume that the long-term consequences of affecting those underlying mechanisms will necessarily be benign (Andrews, Thomson, Amstadter, & Neale, 2012). A meta-analysis of long-term naturalistic studies found a 30% increment in all-cause mortality (deaths) in patients treated with ADMs who were free from cardiac disease (Maslej et al., 2017).

Most prescribing clinicians believe that ADMs work by redressing a deficit in extracellular neurotransmitter in the synapse. This belief is based on the fact that all known ADMs produce an initial increase in synaptic neurotransmitter levels either by inhibiting degradation in the presynaptic neuron (the monoamine oxidase inhibitors [MAOIs]) or by blocking reuptake into the presynaptic neuron (the tricyclic antidepressants [TCAs] and the selective serotonin reuptake inhibitors [SSRIs] and serotonin–norepinephrine reuptake inhibitors [SNRIs]; Belmaker & Agam, 2008). That different ADMs work through different distal mechanisms to affect the same proximal mechanism (synaptic increase) so as to produce the same clinical effect (symptom suppression) lends credence the notion that ADMs redress a neurotransmitter deficit.

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The problem with this notion is that no such deficit exists. It is exceedingly difficult to measure serotonin levels in the intact brain of a living person, so Barton and colleagues used an indwelling catheter to measure 5-HIAA (the primary metabolite of serotonin) levels in the jugular vein (the most direct "downstream" indicator of serotonin levels in the brain). What they found was that 5-HIAA levels are elevated relative to controls in unmedicated persons who are currently depressed (Barton et al., 2008). The same holds true in rodent models of depression in which serotonin levels in the synapse can be more directly assessed (Andrews et al., 2015). Given that ADMs increase levels of neurotransmitters in the synapse, how is it that increasing something that is already in excess can reduce the levels of symptoms in an existing depression?

The answer is that when ADMs increase extracellular levels (up to four times in excess of anything found in nature) they trigger the homeostatic mechanisms that regulate the underlying system to push back (Andrews et al., 2015). People who are not depressed have lower synaptic levels of serotonin than those who are depressed. Putting ADMs on board increases the level of extracellular serotonin initially until the underlying homeostatic mechanisms push back via shutting down serotonin synthesis in the presynaptic neuron and turning down sensitivity in the postsynaptic neuron. (Barton and colleagues also found that 5-HIAA levels measured in the jugular vein were reduced to normal levels in patients stabilized on ADM treatment; Barton et al., 2008.) Mechanistically, putting someone on ADMs is analogous to holding a blow dryer up to a thermostat to turn the furnace down, an effect that lasts for as long as the blow dryer stays on.

The problem with suppressing symptoms in this fashion is that it essentially hijacks the underlying homeostatic mechanisms that might otherwise have brought the episode to an end (spontaneous remission). In effect, patients are likely to stay "in episode" for so long as they stay on medications, thereby keeping them at elevated risk for relapse (three to five times higher than risk of recurrence following recovery) whenever they try to come off (see again Figure 1). Andrews and colleagues refer to this as "oppositional perturbation" and predict that the degree to which a medication class perturbs the underlying neurotransmitter systems should predict the likelihood of relapse when the medications are taken away (Andrews et al., 2011). According to a meta-analysis of ADM discontinuation studies conducted by those authors, this is exactly what happens. Patients who remit on placebo have about one chance in five of relapsing when the pill is taken away; the odds more than double to over 40% when SSRIs are stopped (serotonin only) and go up again to around 50% when SNRIs are discontinued and just below 60% for the TCAs (both classes also affect norepinephrine in addition to serotonin). The likelihood of relapse is highest of all (up to 75%) for the MAOIs that affect all three biogenic amines (serotonin, norepinephrine, and dopamine). It is striking that hypotheses based on oppositional perturbation can so accurately predict differential relapse following differential medication discontinuation.

The risk of using ADMs is twofold. First, if depression is an adaptation that evolved to facilitate rumination in the service of solving complex social problems, then simply medicating that distress may forestall bringing about a resolution to those problems. One is reminded that the maimed squids that felt no pain were the ones most likely to be eaten. Second, if ADMs suppress symptoms via a mechanism that prolongs the underlying episode, then there may never be a good time for a patient to stop. We are twice as likely to medicate a nonpsychotic depression than we were a quarter century ago before the advent of the SSRIs (Marcus & Olfson, 2010; Olfson et al., 2002) and over 85% of patients are kept on ADMs for over two years (Moore & Mattison, 2017). That is exactly what would be expected if you risk relapse whenever you try to discontinue.

The risk is amplified even further by the emerging evidence from cohorts followed prospectively from birth that suggest that prevalence rates for depression are at least twice as high as previously estimated by retrospective epidemiological designs (Monroe, Anderson, & Harkness, 2019). As shown in Figure 2, about half of all persons who ever get depressed do so in response to some major life event and are unlikely to become recurrent ("depression possible") whereas the other half is composed of individuals likely to have multiple episodes ("recurrence prone"). It is likely that depression is the "species typical" response when something truly bad happens to which almost anyone might succumb ("depression possible"), whereas "recurrence prone" individuals likely possess some kind of preexistent diathesis that not everybody shares. To the extent that this is true then it is unlikely that the "depression possible" need to be put on lifetime medications. General practitioners with no psychiatric training write nearly 90% of the prescriptions for the ADMs (almost always SSRIs), raising concerns that they are medicating patients who do not need to be on medications and underdosing the ones that do (Mojtabai & Olfson, 2011). If true, we may be creating a "need" to stay on medications for many people that does not exist in nature.

A Modest Proposal

It remains unclear whether ADMs are iatrogenic in terms of prolonging the life of the underlying episode or if cognitive therapy's apparent enduring effect is an artifact of differential mortality, but both can be tested. What is needed is a trial in which patients are randomized to both conditions as well as to a nonspecific control like a pill-placebo (or other plausible nonpharmacological intervention) that is

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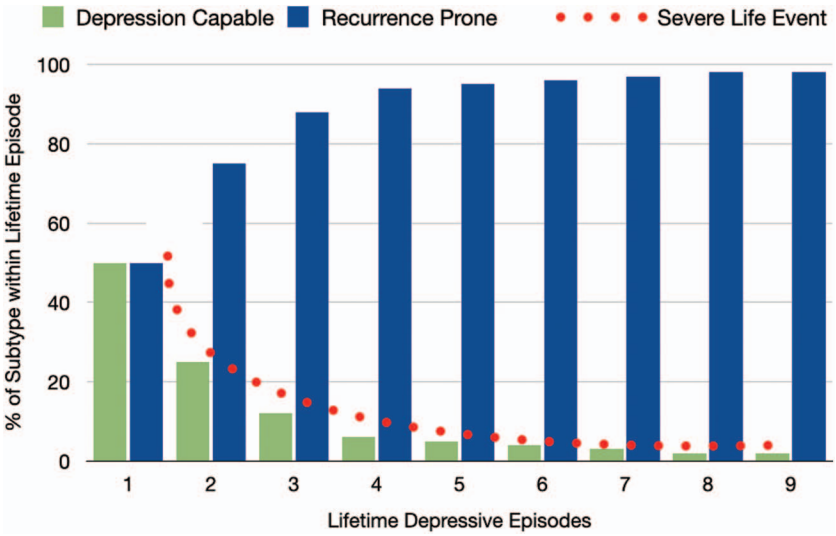

Figure 2. The decreasing association between severe life events and successive recurrences as explained by the dual pathway models. The progressive changes are portrayed in the composition of depression capable versus recurrence prone subtypes as the number of lifetime episodes increases. The weakening association of severe life events with recurrences is depicted by the dotted red line for severe life events that accompanies the diminishing representation of the depression capable subtype as the number of lifetime episodes increases. Reprinted with permission from "Life Stress and Major Depression: The Mysteries of Recurrences," by S. M. Monroe, S. F. Anderson, and K. L. Harkness, 2019, *Psychological Review, 126,* p. 803. See the online article for the color version of this figure.

neither serotonergic nor makes problem solving more efficient. As in the prevention of recurrence trial described earlier, patients would first be treated to remission and then continued on to recovery (Hollon et al., 2014). At that point all treatment would be terminated and recovered patients followed for at least the next year to assess for recurrence (DeRubeis et al., 2020). If cognitive therapy truly has an enduring effect it should do better than the nonspecific control and if ADM is truly iatrogenic it should do worse. Such a design would be provide a clear test, but it does pose both ethical and interpretive issues.

Ethical Concerns

The major ethical concern has to do with randomizing patients to a condition that is likely to be less efficacious than the two presumably active interventions. The response to that concern is that neither cognitive therapy nor ADMs are that specifically efficacious. Patients with less severe depression (at least half of the patients who meet criteria for major depression) do not show a specific response either to psychotherapy (Driessen, Cuijpers, Hollon, & Dekker, 2010) or to medication (Fournier et al., 2010). That is not to say that patients are not more likely to get better if treated than if not, but the majority who do are responding to the nonspecific aspects (pill-placebo and the like). Cuijpers and colleagues used meta-analytic techniques to decompose the proportion of variance in outcome and found that about a third of the change in treatment would have happened anyway (spontaneous remission), half a function of nonspecific processes, and only about a sixth from the specific factors that theorists argue over or that allow medications to go to market (Cuijpers et al., 2012). One can reasonably expect that at least half of the sample randomized (those who are less severe) will do as well in the nonspecific control as they will in either active intervention and that the same will be true for about half of the remaining patients who are more severe (DeRubeis et al., 2005). Moreover, it is a relatively simple matter to monitor symptom levels on an ongoing basis and remove patients from their randomized condition if they are not showing reasonable progress across the course of the trial (this is similar to the "treatment on demand" control used by Weissman et al., 1979).

Interpretive Issues

The interpretive issue is that if (as expected) fewer patients recover in the control condition then comparisons of rates of recurrence will be biased against the active treatments. That is in fact a special case of biasing due to differential mortality (as might be the case if different patients recover in cognitive therapy than in ADM). There are two ways to deal with such an artifact. The first is by using a kind of reverse propensity analysis to identify those patients in the more successful condition(s) that are most like those patients who recover in the less successful control

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at baseline and restrict the primary comparisons to just those patients. That is what was done with data from a study that found an excess of extreme nonresponders in cognitive therapy relative to either behavioral activation or ADM (Dimidjian et al., 2006). Although no formal assessment for Axis II disorders was made in that trial, those patients who were seen by their cognitive therapists as having personality disorders (those patients who were particularly challenging and had a history of troubled interpersonal relationships) were as likely to be found in the other conditions but less likely to show a pattern of extreme nonresponse than they were in cognitive therapy (Coffman, Martell, Dimidjian, Gallop, & Hollon, 2007). The other strategy is to use sustained recovery as the primary outcome (DeRubeis et al., 2020). To meet criteria for sustained recovery, one must remit during acute treatment, recover during continuation, and stay free from recurrence during follow-up. Because all patients are retained in the survival analyses, it is "intention-to-treat" and not susceptible to the biasing effects of differential mortality. Most acute treatment trials use "intention-to-treat" analyses but the tradition in subsequent naturalistic follow-ups has been to restrict the analyses of rates of relapse (or recurrence) to only patients who responded to (or recovered from) treatment, risking bias due to differential mortality.

Moderation

Moreover, it is now possible to do a more sophisticated job of detecting moderation effects than could have been done even in the recent past. Robert DeRubeis at the University of Pennsylvania is in the vanguard of this conceptual/methodological advance. He and his colleagues used multiple regression equations to generate an algorithm using the several moderators of differential response between cognitive therapy versus ADM in his earlier trial with severe depression (DeRubeis et al., 2005) including the disordinal interaction with respect to Axis II disorders already described (Fournier et al., 2008) and ordinal interactions in which more prior medication exposures predicted poorer response to ADM (Leykin et al., 2007) and patients who were married or cohabiting or unemployed or had more precipitants did better in cognitive therapy than on ADM (Fournier et al., 2009). About 30% of the patients would have been predicted by the algorithm to do better in cognitive therapy than on ADM and a different 30% would have been predicted to do better on ADM than in cognitive therapy (DeRubeis, Cohen, et al., 2014). Because about half of each set of patients got randomized by chance to their "optimal" treatment, it was possible to compare those who got their optimal treatment versus those who did not. Across the full sample (including the patients for whom no differential was predicted), optimization would have improved outcomes by nearly a third of a standard deviation ($d = .28$), the magnitude of the drug-placebo difference (Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008). Among the 60% for whom it mattered, the advantage doubled ($d = .58$).

DeRubeis and colleagues are now using methodologically more sophisticated machine learning approaches to generate their algorithms, but the logic remains the same (Cohen & DeRubeis, 2018). As described in their earlier conceptual piece (DeRubeis, Gelfand, et al., 2014), all that is required is to randomize patients to two or more treatment conditions and to generate prognostic indices within each. The average between the two will indicate general prognostic status (from tractable to intractable), whereas the difference between the two will indicate specificity of response with the direction indicating the preferred treatment. Such precision treatment rules (PTRs) take between 300 and 500 patients per condition to stabilize (depending on the degree of differential response and the capacity of the predictive indices to capture those differences) but in larger studies a subset of the sample can be used to generate the PTR with the remainder held out to test it (Luedtke, Sadikova, & Kessler, 2019). Such PTRs could revolutionize the field by identifying the optimal treatment for a given patient (Paul, 1967).

Moderated Mediation

Furthermore, generation of the PTRs as just described should make it possible to do more precise tests of mediation than has been possible to do in the past. It is always easier to detect an effect than it is to explain it. Mediation is inherently a three-variable causal chain (four if treatment process is included) and it is only possible to draw a strong causal inference from the manipulated variable (treatment) to either mediator or outcome, but not from mediator to outcome (Hollon, DeRubeis, & Evans, 1987). Moreover, to the extent that different patients show a different specific response to different interventions (as was the case in DeRubeis, Cohen, et al., 2014), then each set of patients is adhering to different set of causal mechanisms (Kazdin, 2007). Conducting tests of mediation in undifferentiated samples invariably waters down the magnitude of the effects that can be detected. In addition, reverse causality is common; an earlier trial found that cognitive therapy worked through change in cognition to produce change in depression, whereas ADM worked through change in depression to produce change in cognition (DeRubeis et al., 1990). Simply examining mean changes over time and not the pattern of covariation among the indices would have led to drawing the wrong causal inference.

The solution to both of these logical conundrums is to include the PTRs generated to detect moderation as interaction terms in the tests of mediation. Including the PTRs in interactions with the putative mediators accounts for different patients adhering to different mechanisms (individual differences) and including the PTRs in interactions with

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treatment type accounts for reverse causality (Preacher, Rucker, & Hayes, 2007). Both are instances of moderated mediation and it is likely that the vast majority of earlier efforts to test for mediation floundered because they did not take such heterogeneity in individual response into account.

That being said, purely statistical tests of mediation (moderated or otherwise) are likely less than wholly satisfying because they are not based on direct manipulation of the putative mediating variable (much like the shadows on the wall of Plato's cave they represent a depiction of the underlying causal reality and not necessarily the causal reality itself). One particularly convincing demonstration of mediation comes from the animal literature in which Maier and colleagues traced the neural pathways underlying a phenomenon they dubbed learned resilience (Maier, Amat, Baratta, Paul, & Watkins, 2006). Learned resilience is the "flip side" of learned helpless in which organisms exposed to controllable stress appear to acquire a generalized expectation of control that protects against subsequent stressors. Rats have a descending pathway from the ventral medial prefrontal cortex that fires when they have control over a stressor and that in turn synapses on an inhibitory GABA neuron in the raphe nucleus (the location of all the cell bodies in the brain that use serotonin as a neurotransmitter) so as to inhibit the firing of the serotonin neurons in response to stress. The authors further showed that if they cause the descending glutamatergic neuron to fire via pharmacological manipulation they could make rats made helpless via exposure to uncontrollable shock to act as if they were resilient; if they kept the glutamatergic neuron from firing via a different pharmacological manipulation they could make rats trained to be resilient act as if they were helpless. In essence, wiring trumps learning.

Cognitive Therapy Revisited

One of the anomalies in the helplessness literature is that animals made helpless actually outperformed controls when the escape/avoidance response is more complex or requires greater attention to environmental cues (Lee & Maier, 1988). What this suggests is that organisms made "helpless" by exposure to uncontrollable stress may not have given up so much as entertaining more complex hypotheses about how to cope with the situation. Thinking about the causes of a stressor may be useful when one is confronted with an as of yet "uncontrolled" event and sadness does evoke a switch into the energy-expensive Type II thinking (Maslej, Rheaume, Schmidt, & Andrews, 2019). The fact that most depressions remit spontaneously suggests that evolution has provided a mechanism that works to resolve the trigger in most instances (Andrews & Thomson, 2009).

But what accounts for the "recurrence prone" and how is it that some people get "stuck" in their depressions? Longitudinal studies indicate that those individuals who are inclined to make global, stable, internal attributions when things go wrong are particularly likely to become depressed (Alloy et al., 2006) and clinical experience suggests that core beliefs in most recurrent patients revolve around themes of being "unlovable" (for those with affiliative interests) or "incompetent" (for those with more achievement related motivations). The problem with such characterological beliefs is that they point toward no viable behavioral solution. Cognitive therapy encourages patients to consider alternative explanations for their difficulties and to collect evidence (often by running behavioral experiments) to test them systematically. In effect, cognitive therapy does not so much eschew rumination as teach the patient to do so more efficiently, providing a logical structure to define the problem accurately and then come up with a solution (Hollon & Garber, 1990). The existing evidence suggests that for patients to learn to focus more on what they do (behavior) as opposed to what they are (character) not only helps "unstick" the episode but also prevents future ones (Strunk, DeRubeis, Chiu, & Alvarez, 2007). This is something that patients could not do if their "brains were broken" (diseased) and they were unable to reason their way toward a solution and simultaneously out of their distress.

Whether other types of psychotherapy do the same or get there via some other route is an open question. Behavioral activation does not address cognition directly but does generate action plans and appeared to have an enduring effect in the one trial in which it was adequately tested (Dobson et al., 2008). Interpersonal psychotherapy is clearly efficacious in the reduction of acute distress and, although it has yet to be adequately tested with respect to enduring effects, it does addresses problems in relationships to such an extent and in a manner that suggests that it might (Weissman, Klerman, Paykel, Prusoff, & Hanson, 1974, 1981). Anesthetize with ADMs if you must, but teaching patients how to evade life's predators (life stress) is more likely to keep them alive (and free from relapse).

Conclusions

There is reason to believe that depression might be an evolved adaptation that serves to facilitate rumination about complex social issues until some sort of problem-solving resolution is found. To the extent that is true then those interventions that facilitate that function are likely to be preferred. Cognitive therapy and possibly behavior activation appear to have an enduring effect that reduces risk for subsequent symptom return and interpersonal psychotherapy has been shown to improve the quality of relationships. ADMs clearly suppress symptoms but it is possible that they do so at the expense of prolonging the underlying episode.

Although cognitive therapy does appear to have an enduring effect that reduces risk for subsequent relapse or recurrence, differential mortality cannot be ruled out as yet

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as a rival plausible alternative explanation on the basis of the evidence to date. It is by no means certain that ADMs suppresses symptoms at the expense of prolonging the underlying episode, but there is reason to think that they might and potential risk to the larger population is immense. These issues deserve to be resolved empirically and that readily can be done. Medication treatment is so common nowadays and so extended over time that this is a question that needs to be resolved.

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Received April 6, 2020
Revision received July 31, 2020
Accepted August 1, 2020 ■

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