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Major Depression and Its Recurrences: Life Course Matters

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Abstract

Major depression is one of the most prevalent and debilitating personal and public health conditions worldwide. Less appreciated is that depression's tremendous burdens are not shared equally among all who become depressed. Some will suffer recurrences over the rest of their lives, whereas half or more will never have a recurrence. Based on these two distinctive life course prototypes, we propose a subtype distinction for research on the origins and lifetime course of major depression. A pressing goal is to determine at the time of depression's first onset who will follow which clinical trajectory. The lack of recognition of this distinction has resulted in many obstacles, including conceptual biases, methodological oversights, and definitional dead ends. Current theories are reviewed and compared. The implications for contemporary diagnostic controversies, reevaluating research on treatment and prevention, and enhancing the predictive strength of traditionally weak indicators of recurrences and recurrent depression are discussed.

Contents

INTRODUCTION

Major depressive disorder (MDD) is widely recognized as one of the most pressing mental health problems. The global number of incident cases has increased almost 50% over the past 30 years, and more than 264 million people of all ages are currently afflicted (Liu et al. 2020). Recurrences over the life course after an initial depressive episode are particularly problematic; estimates range as high as 75–90% (American Psychiatric Association [APA], 2000, Gotlib et al. 2020, Solomon et al. 2000). The economic costs in the United States alone have increased by 48% over the past

10 years and now exceed $325 billion per year (Greenberg et al. 2021). Indeed, according to the World Health Organization, depression is a leading cause of global mental and physical disability, a major contributor to the global burden of disease (WHO 2021).

Articles on depression typically commence with such despairing themes, citing dire facts and daunting statistics for society and the depressed (Furukawa 2019). On the one hand, this characterization makes good clinical and humane sense. Appealing to the devasting effects of depression provides a powerful motivator for research and action on what can be an extremely destructive mental illness. But on the other hand, this characterization does not make complete scientific sense. At least half of those who become depressed once never do so again (Monroe & Harkness 2011, Monroe et al. 2019). The inconvenient truth this statement uncovers is that the characterization of MDD as an extremely burdensome, often lifelong disorder is the fate of only a portion of the depressed population. However, this fact is conveniently left out of conversations on the research, practice, and policy implications of MDD. It is as if this inconvenient truth about depression broadly writ diminishes the personal gravity or public health urgency of the most disabling and destructive forms of the disorder.

To be clear, we are not suggesting that any form of depression should be dismissed lightly. Rather, we suggest that a useful strategy for reducing the personal and societal burdens of depression is to focus on the forms of the disorder that bear the greatest burdens. Variability in the lifetime course of depression and its recurrences provides a promising focal point for research and action. An unfortunate subset of depressed individuals will have repeated recurrences over their lives. In stark contrast, a larger subset of depressed individuals will never experience any recurrences (Monroe & Harkness 2011, 2012; Rottenberg et al. 2018). This latter lonely fact forces a reevaluation of almost everything presently believed about depression, from etiology through acute phase treatments and recurrence prevention, to questioning the utility of extant research on predicting and preventing recurrences.

Most importantly, these two prominent subsets within the population of depressed people currently are indistinguishable at the time of a given person's initial depressive episode. Their future trajectories cannot be forecasted with any clinical confidence or statistical precision. At the time of first onset, though, clues likely exist that could penetrate this key prognostic impasse about the future lifetime course of recurrences. The consistent emphasis solely upon depression's pervasively deleterious and chronic effects, however, has become so dominant that it eclipses insights to be gleaned from comparative research involving less recurrent forms of the disorder (e.g., people who never have any recurrences). Perhaps now it can be appreciated that by not acknowledging the latter, efforts to mitigate the gravity of the illness for the former are being compromised.

Determining who among the initially depressed will follow which of these two divergent clinical trajectories is a goal of highest priority. To do so, research must begin with the clinical outset, prior to someone having experienced multiple episodes (as multiple episodes and treatments confound comparisons). Individuals who never have any recurrences can be compared at baseline with those who eventually have many; such comparisons may provide information about genetic, endophenotypic, biological, psychological, and social correlates of, and contributors to, recurrences. Successes could enable reimagination and transformation of present-day treatments, resulting in breakthroughs in recurrence prevention and aspirationally leading to dramatic reductions in the personal and societal burdens attributable to the disorder (Monroe & Harkness 2011, Monroe et al. 2019).

PRELUDE: QUESTION AND ANSWERS

The critic could counter, "If it is so terribly important to distinguish depression based on recurrences, why is not more known about this topic already?" It is a fair question, one worthy of several

answers. We introduce these answers, providing a preview of what we address more extensively throughout the article.

Undeniably much research has been conducted on MDD and its recurrences. But the consistent characterization of depression as highly recurrent has distorted the empirical picture, which has led to misleading ideas about depression and its lifetime course. These misunderstandings stand in the way of meaningful progress in research on, and prevention of, recurrences. In the first half of this article, we begin by showing why and how the rates of recurrences in depression have been overestimated. We then detail how past research on predictors of recurrences has been destined to fail, and why the present definition of recurrent depression is empirically unsubstantiated and theoretically useless. With awareness of these inadequacies, it becomes apparent why so little might be known about prognostic indicators for people who bear the greatest burdens of depression over the life course.

In the second half of the article, we turn to present-day theory about who among the initially depressed is most likely to become highly recurrent. Two general theories exist, each drawing upon life stress concepts as central pieces of the explanatory puzzle. Stress sensitization is the long-standing and reigning theory that explains how recurrences develop via a within-person, neurobiological process, which evolves over time in relation to life stress and depressive episodes (Post 1992, Stroud 2018). In contrast, two newly proposed dual pathway models (DPMs) provide a between-person (i.e., subtype) explanation for why one subset among the initially depressed goes on to have many recurrences, whereas another does not (Monroe et al. 2019). Strengths and weaknesses of the two theoretical positions are discussed, particularly regarding their ability to discover who among the initially depressed eventually will become recurrent. Intriguingly, while both stress sensitization and the DPMs invoke stress as a major causal factor, they do so in diametrically opposing ways. Prime opportunities thereby exist to make definitive comparisons between these contrasting viewpoints, which could transform current understanding of the nature of recurrences over the life course. We close with thoughts about depression's inconvenient truth in relation to contemporary diagnostic controversies about MDD, to reevaluating research on treatment and prevention, and to enhancing the predictive strength of traditional indicators of recurrences and recurrent depression.

WHY IS RECURRENCE RISK IN DEPRESSION OVERSTATED AND OVERSOLD?

Depression has not always been viewed as a highly recurrent disorder (Jackson 1986). Beginning in the 1970s, though, the clinical eye and research agenda expanded from a focus on acute, time-limited episodes to a broader temporal gaze on repeated recurrences over the life course. This brought to the forefront a stark realization that many who suffer from depression do so time and again over their lives. It apparently was taken to be a new realization, one that needed to be emphasized and publicized. For example, early on Angst and colleagues (1973, p. 490) opined that "single episodes are extremely rare if the period of observation is significantly extended." Other affirmations followed, reinforcing the theme that single episodes are extremely rare: Depression is a "highly recurrent illness" (Solomon et al. 2000, p. 229) and a "highly recurrent disorder" (Burcusa & Iacono 2007, p. 959). The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) authoritatively declares, "A diagnosis based on a single episode is possible, although the disorder is a recurrent one in the majority of cases" (APA 2013, p. 155). Most recently, Gotlib et al. (2020, p. 174) provided a glimpse of a truth behind all of these statements: "Depressive episodes are recurrent: *In clinical samples*, 75% of individuals with MDD will experience more than one episode (Mueller et al. 1999)" (italics added).

Although depression can be a highly recurrent illness, most often it is not. However, being "highly recurrent" makes for a compelling story about an exceedingly important psychiatric problem. Well intended as this story may be, the estimates have been oversold. In this section, we evaluate research on recurrence rates in clinical and community samples.

Recurrence Rate Estimates: Clinical Populations and Research Practices

In clinical samples, depression is predominantly highly recurrent, as the quote above from Gotlib et al. (2020) indicates. Since people suffering from recurrences are common and readily accessible in treatment settings, they have provided a convenient starting point for research on recurrences. For example, the large-scale Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial enrolled outpatients from 18 primary care and 23 specialty care sites (Hollon et al. 2006). Approximately 74% were experiencing recurrences, and 18% reported 10 or more lifetime episodes. The landmark Collaborative Depression Study (CDS) drew primarily from inpatient (74%) facilities and included far fewer outpatient clinics (Solomon et al. 2000). At the beginning of this project, the majority had experienced at least one prior episode (62%), and 25% had experienced three or more. As we show below, research projects based on clinical samples uniformly report higher rates of recurrences relative to nonclinical samples.

The long-standing CDS is particularly important to single out regarding widely cited and publicly echoed rates of recurrences. Beginning in the 1960s and tracking depressed patients spanning some four decades, the project provides an unparalleled corpus of information on depression over time (e.g., Mueller et al. 1999, Simpson et al. 1997, Solomon et al. 2000). Most pertinent, reports from the CDS supplied the data informing widely cited recurrence estimates published in the DSM-IV and DSM-IV-TR. These DSM estimates became the standard for recurrence estimates that appeared across the world for decades. Perhaps no other source of information has had such a pervasive impact on the perception that recurrences are the norm for depressed people—as opposed to a less common, but clinically crucial, exception.

Based on the data from the CDS, the DSM-IV and DSM-IV-TR indicated that approximately 60% of people who incur a first lifetime depressive episode will develop a second one, 70% of those with a second will suffer a third, and 90% of those with three or more will experience additional, often many more, recurrences (APA 2000, 2013; Mueller et al. 1999; Simpson et al. 1997; Solomon et al. 2000). One might expect debate, at least some discussion, about such highly visible and influential data. To our knowledge, though, these matters have gone mostly without notice (see Monroe & Harkness 2011, Monroe et al. 2019). A close and critical examination of how these estimates were derived is warranted.

Crucially, there appears to be confusion in reporting of the CDS data between an index episode of depression and an initial episode of the disorder (Monroe & Harkness 2011, Solomon et al. 2000). An index episode is a generic term denoting any major depressive episode (MDE) in a person's life. It could be a first episode, but as shown in clinical samples, it is more likely to be a recurrence (e.g., a third episode, a fifteenth episode). An initial episode is a person's first lifetime episode of depression. It may be the only lifetime episode, or it may turn out to be the first of many to come.

In the report by Solomon et al. (2000), recurrences were assessed prospectively over 10 years following each patient's index episode (i.e., ignoring the actual number of past episodes). Of the 318 patients who recovered from their index episode, 202 had at least one recurrence (63.5%). Of these 202 patients with one recurrence, 172 recovered and were at risk for another. Of these 172 patients, 115 had at least a second recurrence (66.9%), and so on (see table 2 in Solomon et al. 2000). To be clear, the recurrence rate for 318 patients who recovered from their index episode

and had at least one prospective recurrence cannot be equated with the recurrence rate for the number of first-episode patients who recovered and had at least one prospective recurrence. Only 38% of that initial sample of 318 patients were in their first lifetime episode. As a consequence of the investigators' approach to the data, recurrence estimates for first-onset cases are almost certainly inflated, and by the same token recurrence rates are likely underestimated for cases with prior episodes (Monroe & Harkness 2011).

Another reason for confusion and inflation of recurrence rates involves differing definitions of recurrence across publications. For example, in one report from the CDS a recurrence was operationalized as a new episode of MDD (Solomon et al. 2000), in another as a new episode of major or minor depression (Lavori et al. 1994), and in yet another as an "episode of affective disorder" (Mueller et al. 1999). In the latter study, 22% of the recurrences were not episodes of MDD but rather episodes of schizoaffective disorder, hypomania, or mania. These alternative definitions may make sense within the context of the goals of any particular study, but they are easily confused under the common label of a recurrence and can be indiscriminately equated across investigations. The quest to obtain accurate rates of recurrence, and to discover early predictors, obviously is compromised when different clinical phenomena are permitted within the definitional boundaries of a recurrence (Monroe & Harkness 2011).

Recurrence Rate Estimates: Nonclinical Populations and Research Practices

As indicated, clinical samples include many severe and chronic cases, which are associated with an increased prevalence of recurrences. General population samples include less severe and chronic cases, which are associated with a decreased prevalence of recurrences. Notably, these latter investigations overcome important sampling biases (e.g., the "clinician's illusion"; Cohen & Cohen 1984). General population studies therefore are a necessary counterpart to clinical samples for obtaining a more complete picture of depression and its recurrences.

Based on a general population sample of 687 nondepressed individuals who had a lifetime history of MDD, Hardeveld et al. (2013) examined prospective recurrences over a 3-year follow-up. At baseline, recency and severity of the prior MDE were assessed retrospectively; the investigators reported an overall cumulative recurrence estimate of 42% at 20 years. Notably, the sample was diverse with regard to past episodes (47% single versus 53% recurrent). As with the CDS data, this indicates that for first-onset cases the recurrence rate would be even lower than 42%.

Three other population-based studies reported recurrence rates specifically for first-onset cases of depression. Analyzing data from the Baltimore site of the Epidemiologic Catchment Area Study, Eaton et al. (2008) followed 92 people subsequent to a first lifetime onset of MDD. They reported that approximately 50% of these first-onset cases recovered and did not have additional depressive episodes (up to a maximum follow-up period of 23 years).

A second longitudinal investigation employing a geographically defined population-based sample is the long-standing Lundby Study (Mattisson et al. 2007, Nöbbelin et al. 2018). Beginning in 1947, this cohort study followed 3,563 participants. The course and outcome were detailed for 344 individuals who developed their first episode of depression between 1947 and 1997. These incident cases were diagnostically heterogeneous (about 60% were MDD, and the others were subtypes of depression, such as depression not otherwise specified or adjustment disorder with depressed mood). Mattisson et al. (2007) commented that "[t]he probability of remaining free of recurrence was about 60% in the whole sample" (p. 889) and emphasized the lower rate of recurrence relative to patient samples.

Finally, the Dunedin Multidisciplinary Health and Development Study ($N = 1,037$) was based on a representative birth cohort (1972–1973) of nonclinical participants followed to age 32 (96%

retention rate) (Moffitt et al. 2010). Remarkably, lifetime prevalence statistics based on this informative research design were approximately twice the rates found in retrospective surveys. For depression, these investigators found a cumulative lifetime prevalence of 41.4%. Closer examination revealed that 60% of lifetime depressed cases were diagnosed at only one of the ongoing longitudinal assessments. Further, the authors noted that "retrospective surveys may undercount primarily individuals who have relatively short-term disorder or single episodes" (Moffitt et al. 2010, p. 906).

The findings of Moffitt et al. (2010) affirm again that many, if not most, incident cases of MDD in the general population do not have recurrences. Of added and unique value, the findings from this rare design strongly suggest that any measurement error for lifetime risk of depression works in favor of (*a*) increasing the proportion of single lifetime cases in the depressed population (e.g., perhaps up to 60%) and (*b*) decreasing the proportion of suspected false-negative recurrent cases (e.g., single lifetime cases who are recurrent cases owing to underreporting of episodes).

All four studies provide consistent evidence of a lower rate of recurrence for first-onset cases of depression in general population samples relative to rates based on an index episode in clinical samples. We are unaware of any evidence from studies indicating anything otherwise. Combined, these studies converge to indicate that roughly 50–60% of first-onset episodes of MDD in the general population never have any recurrences. The population prevalence of an acute and nonrecurrent subgroup of depression is at least equal to, and most likely exceeds, that of any "recurrent" subgroup.

The debate must move beyond whether depression is highly recurrent or not. As presently defined, diagnosed, and classified, depression is an unknown mixture of both (Monroe & Harkness 2012). The discussion should start to explain what this signifies, and efforts should be made to detect prognostic indicators early in the lifetime course for who will and who will not have many recurrences.

WHY HAS RESEARCH ON PREDICTORS OF RECURRENCES FAILED (MOSTLY)?

The paucity of predictors of recurrences is not for any lack of effort. Numerous studies have tackled the topic (e.g., Buckman et al. 2018, Burcusa & Iacono 2007, Hardeveld et al. 2010). As shown below, entrenched definitional and methodological shortcomings have blocked progress. A major obstacle, though, is conceptual: the failure to recognize and then capitalize on the fact that many people who initially become depressed never become depressed again.

Research on the origins of recurrences with a mindset that everyone who becomes depressed is highly susceptible to recurrences represents a specific conceptual stance, one that has received extensive research attention. It has its own particular implications for guiding research. Attempting to understand the origins of recurrences with knowledge that many who become depressed will not have recurrences represents a very different conceptual stance, one that has hardly received any attention to date. It, too, has its own distinct implications for guiding research. To discover predictors of who will have recurrences following an initial episode, a comparison group of people without recurrences seems indispensable. It is this very comparison that is lacking from the existing evidence base.

Below, we first address at a microlevel basic concerns in defining a recurrence, and then we discuss at a macrolevel broader problems with research designs. Both topics reveal why it has been so difficult to discover predictors for determining who among the initially depressed will and will not have recurrences.

Predicting a Recurrence: Definitional Considerations

To discover predictors of a recurrence, what qualifies as a recurrence must be stipulated as clearly as possible. Without a valid dependent variable, all else is destined to fail. As explained next, though, defining and operationalizing a recurrence is not so obvious or easy to clearly stipulate.

Definitional issues: a recurrence. At the microlevel, defining a recurrence is a surprisingly complicated matter. For a simple example, we have foreshadowed inconsistencies in what counts as a recurrence by pointing out alternative definitions employed in different CDS analyses (a new episode of MDD, an episode of major or minor depression, etc.; see above) and noting that predictors of recurrence (or the lack thereof) will be inconsistent across inconsistent definitions of a recurrence. This particular example, though, could be redressed relatively readily. The definition simply could be standardized—e.g., requiring a new episode of MDD. But this begs the next question: What qualifies as a new episode of MDD?

Defining a new episode of MDD is complicated because it is actually a multistep process. It first requires defining an episode of MDD and, second, defining when an episode of MDD qualifies as new. For the latter, there are two additional prerequisites: a previous MDE and a recovery from the previous MDE. As the end point in a sequential process, any definition of a recurrence is heir to the individual liabilities and validities of each definitional prerequisite as well as to the entire sequential definitional process (Monroe & Harkness 2011).

For instance, recovery is not an empirically certified construct but rather a working premise that depends substantially upon the chosen parameters. It is defined by (*a*) degree of initial symptomatic improvement, (*b*) degree to which the symptomatic improvement is sustained, and (*c*) duration of the sustained symptomatic improvement. How these individual definitional components are operationalized yields highly variable clinical outcomes for defining recurrences. For example, if the degree of symptomatic improvement is low or high (4 symptoms versus 0 symptoms), or the duration of sustained improvement is low or high (e.g., 8 or 24 weeks), the result will be dramatically different rates of recurrences (e.g., Frank et al. 1991; Monroe & Harkness 2011, figures 2 and 3). Without any gold standard for defining recovery, and without research validating any proposed standard, no valid standard for defining a recurrence exists.

Recognizing serious inconsistencies in defining change points over the course of a depressive episode, a precedent-setting article (Frank et al. 1991) sponsored by the MacArthur Foundation proposed a consensually derived system for defining and operationalizing recurrences (and related clinical constructs; see also Rush et al. 2006). Conceptually, a recovery implies a period of sustained symptom improvement, such that continued well-being is expected and an MDE is not likely to occur in the near future; if one does occur, it is deemed to be a new episode (i.e., as opposed to a relapse "back" into the original episode) (see Frank et al. 1991, Monroe & Harkness 2011). Drawing upon an updated analysis of the literature, a follow-up consensus conference provided further recommendations for operationalizing recovery (Rush et al. 2006). "Based largely on logic, clinical impression, and consensus," the authors suggested that recovery requires a sustained symptomatic improvement for 4 months following remission, with symptomatic "roughening" permitted (Rush et al. 2006, p. 1850). Both Frank et al. (1991) and Rush et al. (2006) were clear about the provisional nature of their recommendations; Frank et al. (1991, p. 855) enthusiastically called for "others to challenge [their] tentative suggestions with alternative conceptualizations and for empirically derived criteria."

For several decades, these recommendations have guided wide-ranging research on depression, with the consensus-based definitions being "paramount driving forces for consistency in MDD research as well as in clinical practice" (de Zwart et al. 2019, p. 544). They have done so based

mostly on faith and face validity without much empirical evidence or critical analysis (cf. Monroe & Harkness 2011). Recently, however, de Zwart et al. (2019) published a much-needed systematic review of the accumulated evidence on the validity of the MacArthur consensus definitions of remission, recovery, relapse, and recurrence.

Evaluating 56 qualifying studies (including 39,315 participants), these authors concluded that (*a*) for episodes less than 12 weeks, spontaneous remission rates are very high, and therefore 2 weeks is too short for the minimum MDE duration criterion; (*b*) the operationalization of remission is too lax (≤7 symptoms), resulting in many false negatives (i.e., individuals who are characterized as in remission but still meet criteria for MDE); and most fundamentally for present purposes, (*c*) there was no evidence for a duration threshold distinguishing remission from recovery. Instead, the most common pattern was gradual improvement in prognosis over time. With reference to the latter point, the authors argued that "the whole concept of these duration criteria must be rejected," that it "is a model that lacks empirical support," and lastly, that "it is of no additional value to the patient or clinician as the assumed origin of the reoccurring symptoms has no implications for treatment or prognosis" (de Zwart et al. 2019, p. 559).

The review by de Zwart et al. (2019) is an important initial contribution toward greater empirical clarity regarding these fundamental conceptual and definitional matters. The general implications for recurrences, and hence for predictors of recurrences, are evident. If the duration criterion for defining an MDE is lengthened, the symptom criterion for defining remission is reduced (and hence for defining recurrences), and the duration criterion for distinguishing remission from recovery has no prognostic utility, then a very different clinical picture emerges for what qualifies as a recurrence (e.g., Monroe & Harkness 2011, figures 2 and 3). If valid, these recommendations would result in very different rates for recurrences and most likely in very different predictors of recurrences. More broadly, the provisional nature of current practices for defining recurrences needs to be recognized, and as Frank et al. (1991) and Rush et al. (2006) unambiguously indicated, research along these lines is sorely needed.

Definitional issues: recovery assumptions. In addition to providing guidelines for defining recovery, Frank et al. (1991, p. 853) stated that the term recovery "is used to designate recovery from the episode, not from the illness per se." Despite the absence of any theoretical or empirical rationale (see de Zwart et al. 2019, Monroe & Harkness 2011), this comment has been adopted by, and reiterated verbatim in, subsequent consensus reports (e.g., Rush et al. 2006, Tohen et al. 2009). The statement appears to coast on the rhetorical allure of, while simultaneously reinforcing, the popular theme of depression as a highly recurrent disorder.

As such, the statement prematurely forecloses on alternative ways to conceptualize matters. Relations between a recovery, an episode, a recurrence, and an illness are foreordained, codified, and finally certified—without substantive evidence. But consider a person who first becomes depressed at age 24 following a devastating marital breakup. Suppose the same person becomes depressed a second time at age 84, without environmental adversity, with white matter hyperintensities on a computed tomography scan. There is a return of signs and symptoms that can qualify as depression, but is there a return of the same disorder? Whether this case represents a recurrence should be open to question, analysis, and debate (Monroe & Harkness 2011). Depression is understood to be heterogeneous, at least one meaning of which is that there are etiologically distinct subtypes of the disorder; it would seem prudent to remain open to the idea that recurrences can be etiologically heterogeneous too (Monroe & Anderson 2015, Monroe et al. 2019). In a manner similar to recovery silently dictating any definition of a recurrence, illness now becomes a silent but equally dictatorial construct operating behind the entire production for conceptualizing and defining all recurrences.

More fundamentally, the comment "recovery from the episode, not from the illness per se" (Frank et al. 1991, p. 853) is directly at odds with the more up-to-date and representative general population recurrence rates reviewed above. It clashes with the fact that in many individuals, depression occurs only once in a lifetime. How can so many people never have another episode yet still not recover from the illness? Perhaps the premise could be more usefully considered for the subset of people who have many recurrences.

Predicting a Recurrence: Methodological Issues

Broadly speaking at a macrolevel, the generic objective has been to investigate factors that distinguish depressed persons according to the number of previous episodes that they have experienced. It is generic in the sense that each recurrence is considered, and statistically analyzed, equivalently (e.g., a first recurrence is weighted the same as a fifth or fifteenth). A second, more focused research tradition has prioritized recurrences that occur early in the lifetime course based on the assumption that earlier recurrences are more informative than later ones. We address each tradition in turn.

Predicting a recurrence: generic studies. Common research practices have evaluated putative risk indicators associated with a current (index) episode (i.e., cross-sectional designs) or with a future episode (i.e., prospective designs). Risk indicator associations are typically made between single and recurrent groups or over the full distribution of lifetime episodes (e.g., Hollon et al. 2006, Kendler et al. 2000, Monroe et al. 2007, Solomon et al. 2000).

Investigating correlates of a recurrence in samples of people who already have had many recurrences, however, is most likely to be unproductive. For example, a person with 7 recurrences may not differ substantively from someone with 12 recurrences. Both are already highly recurrent, likely have similar liabilities to recurrences, and are likely to have more recurrences. Indeed, the person with 7 recurrences probably will become the person with 12 recurrences over time (and the person with 12 recurrences once was a person with 7). Putative predictors related to recurrences between people who already have had many recurrences become more difficult, if not impossible, to discern as the number of lifetime episodes rises (Monroe & Harkness 2011). People who will not have recurrences are needed.

Generic research designs are "recurrence heavy." They include mostly patients who have had often many recurrences and who, thus, are already highly recurrent. The statistical analyses are overpowered to detect predictors of minimal theoretical interest (e.g., predictors of a recurrence in patients having 5 versus 6 or 12 past episodes) and underpowered to detect predictors of maximum import (e.g., predictors of a recurrence in patients having 0 versus 1 past episode). These studies compare apples with apples (recurrent cases with recurrent cases), whereas in this context comparing apples (recurrent cases) with oranges (nonrecurrent cases) is needed (Monroe & Harkness 2011).

There is another substantial limitation of the generic design. Much research on recurrences has been cross-sectional, largely confined to information about patients who vary by past number of depressive episodes (e.g., Hollon et al. 2006). This means that people who will not have recurrences cannot be discerned and thus cannot be directly compared with those who will have recurrences. Those without recurrences simply disappear from these research protocols, their absence having gone unnoticed. All that can be inferred is how people who presently differ by the number of past episodes, assessed at an arbitrary point in the lifetime course of recurrences, differ from one another with respect to risk indicators. Nothing directly can be inferred about how people who will have recurrences differ from those who will not (Monroe & Harkness 2011).

A consolation prize from these generic studies is the oft-repeated mantra that past episodes predict future episodes. But this iconic indicator is problematic as well. It is likely true for those who have had many episodes, but it is not true for those who have had just one. Of the latter group, many if not the majority will never have additional episodes. Provocatively considered, does this suggest that the risk of recurrence for the single-lifetime-episode group could be lower than that for the population of never-depressed people? To address these matters, we now turn to research that has been more appropriately designed, but still imperfectly so, on depression and its recurrences.

Predicting recurrences: first onset versus recurrences. Research designs that compare first-onset with recurrent cases to predict recurrences represent a significant advance over the generic recurrence studies. Depending on how the strategy is implemented, though, some studies are better suited than others for detecting prognostic relations.

The most straightforward and easily conducted studies are cross-sectional, comparing first-onset cases with recurrent cases on a variety of predictors. The shortcoming of these designs is the heterogeneity of recurrence risk within the population of the first depressed. Since approximately 50% of first-onset cases go on to have one or more recurrences, they will be single lifetime cases only temporarily, and thus in reality they likely share the same high liability to depression with people who already have had recurrences. If so, these false-positive single lifetime cases would attenuate prognostic comparisons of initial predictors between true single lifetime cases and recurrent cases. A significant lesson to be learned from these studies is that, although commonly confused, first-onset cases are not at all the same as single lifetime cases (Monroe & Harkness 2011).

A similar but less pronounced heterogeneity problem exists for a first recurrence. Many people who have a recurrence will never have another episode. They may be false-positive recurrent cases (i.e., their liability is closer to that of the single-lifetime-episode group). As a result, predictors of recurrences also will be harder to find because of this subgroup's misleading inclusion as recurrent. This further supports the contention that a clear majority of people who ever become depressed in the first place do not have a highly recurrent illness (see also Buckman et al. 2018) and further explains why prognostic indicators might have been so elusive.

With the insights afforded by time, longitudinal studies have the capability to better identify valid single lifetime cases and recurrences. Given that about 50% of first-onset cases eventually will "convert" to recurrent cases, while the other 50% will remain single-episode cases, early errors in identification are corrected naturally over time. The longer the follow-up is, the more secure and valid the respective groupings become (perhaps within 6 years; Monroe & Harkness 2011, Monroe et al. 2019). As cited above, several longitudinal studies provide more representative rates of recurrence following a first lifetime episode (Eaton et al. 2008, Mattisson et al. 2007, Moffitt et al. 2010). Unfortunately, most of these studies have not provided data on specific risk measures taken at the time of the first lifetime episode to predict a recurrence (cf. Nöbbelin et al. 2018).

Summary

From a microlevel perspective, how a recurrence is conceived and defined fundamentally drives the ability to detect recurrence predictors. Contemporary concepts and procedures, however, rest on complex and largely unproven assumptions. More recent theory and empirical research reveal opportunities for investigating and updating these procedures (de Zwart et al. 2019, Monroe & Harkness 2011). Improved definitions and operational guidelines provide optimism and promise for future research on discovering who among the initially depressed may have many subsequent episodes.

From a macrolevel perspective, research designs for investigating recurrences have not lived up to their potential. Generic designs are insensitive for discovering predictors of recurrences, as all recurrences are considered and analyzed equally. Prognostic indicators easily may have gone unnoticed. Research designed to prioritize recurrences early in the life course of depression, too, has been insensitive for detecting predictors. Since many incident cases will have one or more recurrences, their presence within the first-onset sample would dilute predictors associated with those who will never have any recurrences. To repeat, first-onset cases are not the same as single lifetime cases (i.e., a nonrecurrent subgroup).

Early predictors of who will and who will not have recurrences likely exist, but for the most part such predictors have eluded detection. Improvements in concepts and practices may provide guidance to assist in their discovery, which we begin to address in the following sections.

THE VERY CURIOUS CASE OF CONCEPTUALIZING AND DEFINING RECURRENT DEPRESSION

Pausing for the moment and taking a big step back, we ask what the ultimate objectives for research on depression and its recurrences might be. Certainly, a clinical objective is to prevent each recurrence in any individual who suffers from a depressive episode. To assist with this, a scientific objective is to predict a recurrence in anyone who has experienced a depressive episode. But do existing theory and research on these objectives address the forms of depression that indeed bear the greatest burden? We think not, and we assert that this is a most important matter to resolve.

Individual recurrences indisputably are one piece of the broader landscape of a lifetime course of depression. However, attention to each individual recurrence alone may be insufficient (think trees), impeding attention to the forms of depression that bear the greatest burdens over the life course (think forest). By focusing on recurrences one by one, the research community may have overlooked broader scientific and clinical objectives: to predict and prevent recurrences for those who bear the greatest burdens.

Skeptics might question this assertion, contending that nothing novel is being proposed, that a wealth of information exists and is evolving about recurrent depression ("Been there, still working on it"). This is understandable and is a pivotal point that is central to our thesis. In a technical sense, too, these skeptics are correct. But the technicality hinges upon whether the current definition of recurrent depression adequately captures the population of depressed individuals who bear the greatest burdens of depression over the life course. We next take a big step forward to reveal how the present definition of recurrent depression fails to live up to this expectation and directly stands in the way of the clinical and scientific objectives for understanding what recurrent depression might actually be.

Defining Recurrent Depression: Theory and Evidence

It is unclear why or how two lifetime episodes became the threshold instantiating the definition of recurrent depression (Monroe & Harkness 2011). There is no conceptual rationale that can be readily discerned; no convincing theoretical argument has been explicitly put forward. Perhaps the closest justification comes from the DSM-5: "A diagnosis [of depression] based on a single episode is possible, although the disorder is a recurrent one in the majority of cases" (APA 2013, p. 155). But this is only a proclamation, devoid of any supportive information.

Absent theoretical justification, empirical data should inform any definition of recurrent depression. Yet the measurement decisions are not just questionable (Flake & Fried 2020) but in fact appear to be nonexistent. Within clinical samples, some after-the-fact evidence can be marshalled (e.g., Hollon et al. 2006). Within community samples, though, the matter remains entirely

uncertain. The DSM-5 statement that "the disorder is a recurrent one in the majority of cases" (APA 2013, p. 155) belies compelling evidence to the contrary based upon these community samples (e.g., Eaton et al. 2008, Moffitt et al. 2010). Clearly, many questions can and should be raised about the theoretical and empirical bases justifying the contemporary definition of recurrent depression.

On Defining Recurrent Depression and Defining a Recurrence

As explained above, recurrent depression is defined by prerequisite concepts and definitional criteria (i.e., an episode of MDD, recovery, a new MDD episode). Any definition of recurrent depression, though, needs to build upon these definitional prerequisites. To have theoretical or practical value, the term requires added meaning unique to its privileged status as a superordinate concept.

A potential fatal flaw of defining recurrent depression based on two depressive episodes is that it essentially confounds a single recurrence with recurrent depression. A recurrence is defined as an episode of major depression happening at any time following recovery from a previous depressive episode. Recurrent depression also is defined by an episode of major depression happening at any time following recovery from a previous (albeit initial) depressive episode (e.g., APA 2013, Burcusa & Iacono 2007). A single recurrence defines recurrent depression. Anyone who meets the criteria for recurrent depression is simply someone who has had a recurrence; no one can experience a recurrence without being designated as having recurrent depression. Nothing substantively or semantically is gained with the term "recurrent depression" beyond the information already supplied by knowledge about a recurrence. There is no superordinate concept.

Conceptualizing Recurrent Depression

In contrast, in theory a recurrence and recurrent depression substantively differ. A recurrence simply is one instance of another MDE following recovery at any point in someone's life. The inferred causes of any particular recurrence remain unspecified and are likely heterogeneous. As a construct, however, recurrent depression represents much more than a single recurrence and denotes many collective MDEs over a lifetime. The inferred cause of recurrent depression is high liability to depression. By shackling the definition of recurrent depression to that of a single recurrence, the important conceptual distinction between the two is lost. Functionally they differ largely in name only.

By rebranding a first recurrence as recurrent depression, however, present definitional practices create the appearance of something different, something more, something new. But with this practice, the "emperor" (recurrent depression) has no clothes (at least no new clothes). Viewed in this way, it seems inescapable that predictors of recurrent depression have been obscured by predictors of individual recurrences for people who already have had many recurrences (i.e., have recurrent depression). In this sense, individual recurrences become red herrings. Might the inability to determine, at the time of depression's first onset, who will and will not have many recurrences be the consequence of a fatal flaw in defining recurrent depression? As wisely observed, it is important to recognize "the difference between knowing the name of something and knowing something" (Feynman 1999, p. 5).

CONCEPTUALIZING NONRECURRENT AND RECURRENT DEPRESSION: BEYOND TWO EPISODES

Virtually all research on depression, its recurrences, and de facto recurrent depression adheres to the authoritative precedent of dichotomizing the population of depressed people solely based

upon a second episode. Construct validation, though, typically draws upon multiple indicators (Cronbach & Meehl 1955). Single-episode cases of depression and recurrent ones, however, basically require one "perfect," pathognomonic indicator. For single-episode cases, this is a lone episode of MDD; for recurrent cases, it is a second lifetime episode of depression. An arbitrary and invariant number, initially intended to index a construct resembling recurrent depression, appears to have become the construct itself (Brown & Harris 1986, Kendler 2016, Monroe & Harkness 2011). Having two lifetime episodes, however, does not translate to an absolute or natural number, such as pi or *e*. Two is a single fallible number, which is insufficient for the theoretical objective. The exact number of episodes is less useful than the degree to which any particular number reflects an underlying liability to recurring episodes of major depression over time (i.e., recurrent depression).

We have shown, though, that a static definitional approach does not do justice to the progressive evolution of the two subgroups over time and their eventual and final life course phenotypes (i.e., nonrecurrent and recurrent depression). Ideally, the end points of life course phenotypes would be useful descriptively to inform concepts and to help define recurrent and nonrecurrent depression, not arbitrary time points along the way. Current definitional approaches mostly have it temporally backward. Consequently, to predict and prevent recurrences for those who bear the greatest burdens of depression, we do not yet know what to look for—what the life course phenotype(s) of recurrent depression might look like.

An obvious obstacle is that final lifetime trajectories of depression are unknown and, admittedly, are difficult to come by. At present, about all that can be said with some confidence is that many people have only one lifetime episode and that some have too many to count. How well these two extreme life course trajectories represent all depressed people is another key question. A second episode, though, is currently the only indicator separating two subgroups. We next propose alternative ways of thinking about episode history and recurrence futures and speculate on possible complementary indicators for redefining recurrent depression.

Nonrecurrent Depression

The single-lifetime-episode group is quintessentially nonrecurrent. But why can't they have any recurrences? Since they are proven depression capable, they would seem susceptible to another episode under conducive circumstances. They are just relatively unlikely to do so individually and collectively (Monroe & Harkness 2011, Monroe & Simons 1991, Patten 2018). These individuals are not prone to recurrences. A softer demarcation for the number of episodes—a more flexible matter of degree rather than an invariant decree—is worth entertaining.

How many episodes would be acceptable, and how many would be too many? On what theoretical or empirical grounds should this decision be made? First, the previously presented case of someone with two lifetime episodes of depression, separated by 60 years with different causes, underscores definitional hesitations about two episodes. Second, someone with only two lifetime episodes, yet in whom the sole recurrence happens shortly after recovery, raises similar concerns. Lastly, the fact that the second-largest subset of the depressed population (after single lifetime depressed cases) probably has only two lifetime episodes furthers the argument (Monroe & Harkness 2011). These clinical examples and epidemiological data do not square with the experience of depressed people who bear the most burdens of depression over the life course (despite having two lifetime episodes). These three points alone perhaps afford a stronger case against two lifetime episodes than yet has been marshalled in support of the well-established practice. Past history of depression no doubt is useful but not entirely trustworthy.

If someone is capable of a second MDE, might life circumstances possibly—just not probably—provoke a third as well? And so on. On numerous counts, it is worth evaluating whether one

lifetime episode is too dogmatic and restrictive, an imperfect indicator for nonrecurrent depression (i.e., someone with a low liability to recurrences). By the same token, this directly implies that having two lifetime episodes is too inclusive an indicator for recurrent depression (i.e., someone with a high liability to recurrence; Barbuti et al. 2019, Goodwin & Jamison 2007). We next turn to this topic.

Recurrent Depression

Once the questionable definition of two lifetime episodes for recurrent depression is abandoned, the objective becomes more obscure. The task can be likened to climbing a mountain, not knowing what vistas will appear over the next ridge and what new observations will come into view. There are untold ways someone might experience recurrences over a lifetime. What recurrent depression might look like amid this uncharted territory remains to be discovered. A first step is with data.

Descriptive data on recurrences and their timing over the life course provide a starting point with a theoretical eye toward distinguishing those who likely bear most of the burdens of depression over time. Recent longitudinal studies drawing upon population-based samples on recurrences would appear to be capable of providing empirical guidance and substance for delineating recurrent and nonrecurrent subgroups (e.g., Mattisson et al. 2007, Moffitt et al. 2010). Retrospective research, too, could supply useful preliminary observations. For example, clinical information about people who have had many episodes could shed light on age at initial depression onset, timing of recurrences, severity of recurrences, associations with stressors, and so on, compared with the clinical trajectories of people with very few lifetime episodes. Although retrospective research has limitations, the likelihood of obtaining a complete history of episodes over the life course may well be greater than a complete follow-up (Oepen et al. 2004). It would take less time and resources and could provide much-needed clues.

Ideally, based on an end point analysis, what might a final distribution of lifetime episodes look like? Without much question, from an initial onset through at least a few recurrences, the number of cases will decrease with each subsequent recurrence. The illuminating question, though, is what happens thereafter. Might the distribution continue to decline linearly or asymptotically skew positive, eventually reaching a plateau with too many to count? Or might some who become depressed progressively move rightward on the graph over time, eventuating in a bimodal distribution revealing a cleaner depiction of recurrent and nonrecurrent subgroups? These two hypothetical possibilities are portrayed in **Figure 1**.

More generally, multiple indicators are needed for elaborating a nomological network, thereby "increasing the definiteness of its components" for identifying a construct of recurrent depression (Cronbach & Meehl 1955, p. 290). We next propose additional information of potential value for defining the exceedingly important clinical group of people who will have lifelong problems with recurrences (Monroe et al. 2019).

CONCEPTUALIZING RECURRENT DEPRESSION: MINING EPISODE INFORMATION

More information can be extracted from past history to potentially bolster its prognostic utility. One possibility is timing of the episodes. A lifetime can be a long time, and 60 years between episodes appears too permissive for defining recurrent depression. People who have recurrent depression possess a high liability for doing so, which would likely be manifested in frequent episodes with relatively short periods of wellness in between. After recovery from an initial lifetime episode, do people who eventually become recurrent have shorter intermorbid well periods relative to those

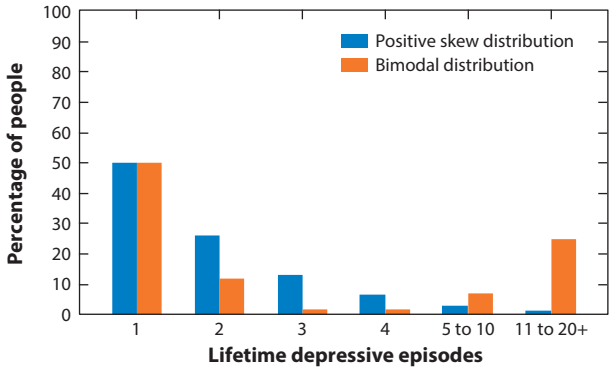

Figure 1

End point life course epidemiology of depression. Two hypothetical distributions of the projected percentage of people who experience depression by the final number of lifetime episodes.

who may have another episode but do not become highly recurrent? A recent longitudinal study found that depressed individuals who became highly recurrent indeed had consistently shorter intermorbid well periods between recurrences, even after the first episode (Anderson et al. 2016). Further research is warranted, but these findings are an example of how additional information about prior episodes may have predictive value, as well as proof of concept for time to first recurrence as a potential indicator of high recurrence likelihood.

The stability of symptoms from one episode to the next might be another indicator for subtype classification (Kendell 1974, Lamers et al. 2012). In view of the heterogeneity of depression, it is not surprising that it has been difficult to demonstrate phenotypic consistency over episodes (Rodgers et al. 2014, Young et al. 1987). Yet other ways of parsing heterogeneity (i.e., recurrent versus nonrecurrent subgroups), and incorporating factors other than symptoms alone (e.g., major life stress; Brown et al. 1994, Frank et al. 1994), could provide leverage for improved subtype determination (Ulbricht et al. 2018). An elevated liability to depression might result in greater syndromal consistency across episodes. For example, a lower liability to depression might yield less consistency owing to distinctive consequences of different types of severe events that provoke their onset (Finlay-Jones & Brown 1981, Fried & Nesse 2015, Kendler et al. 2003).

As with the timing of episodes, syndromal consistency could supplement episode history for signifying early on the likelihood of recurrent depression. For instance, many people who have a second episode will never have another one, and perhaps they would be better categorized as nonrecurrent. But based on episode history alone, they would be false-positive recurrent cases. Episode timing and syndromal consistency conceivably could help to offset the imperfections of the fallible episode history indicator. Depending on how imperfect these additional indicators might be, they at least might provide a note of prognostic caution and at best might provide a prognostic correction.

Even more information domains could be mined for defining the subgroups. Thus far, however, the indicators discussed are descriptive. They are believed to reflect (or go with) the hypothetical constructs. They are silent about causal factors (i.e., number of episodes does not cause a subtype of depression). There is a major causal factor, though, that could be more definitive for understanding subgroup differences in the origins of depression and its recurrences, which in turn could represent a major advance toward predicting who among the initially depressed will become recurrent. We examine this promising topic next.

RECURRENT AND NONRECURRENT DEPRESSION: WHAT'S STRESS GOT TO DO WITH IT?

Abundant research has documented that adverse life events are potent causes of MDD (e.g., Hammen 2005, Mazure 1998, Monroe et al. 2014a). In particular, highly threatening or severe life events are especially potent for provoking onset (e.g., job loss, extramarital affair, divorce; Brown & Harris 1978, Kendler et al. 1998). Even with other risk factors taken into account, severe life events remain among the strongest predictors of depression onset (e.g., Daley et al. 2000; Kendler et al. 2002, 2004).

Of special interest for understanding the recurrent and nonrecurrent subgroups, a second research literature indicates that the association of severe life events with depression onset is moderated by number of prior episodes (e.g., Hammen 2018; Kraepelin 1921; Post 1992; Stroud et al. 2008, 2011). Specifically, severe life events occur most frequently before first episodes and are progressively less likely to occur before successive recurrences. This observation might provide key insights into the causes of depression and its recurrences (Monroe et al. 2019). How might the changing association of major life stress over successive recurrences be explained, and how might such explanations point the way to a better understanding of who among the initially depressed will and will not become recurrent?

MAJOR LIFE STRESS AND ITS RECURRENCES: A TALE OF TWO THEORIES

In this section, two major theories that have focused on major life stress to explain recurrences in MDD are outlined, briefly evaluated, and then compared. For present purposes, we chiefly confine the analysis to the utility of the two approaches for understanding who bears the greatest burdens of depression and for ascertaining who they might be at the time of initial MDD onset. A more thorough analysis is available elsewhere (Monroe et al. 2019).

Stress Sensitization: Introduction and Evaluation

Stress sensitization (i.e., the kindling hypothesis) has been the reigning theory, designed first to account for the observation that major stress becomes less common over successive episodes, and then to provide a hypothetical mechanism via which liability to recurrences develops over time (Post 1992, Stroud 2018). As a consequence of major stressors triggering early depressive episodes, the theory proposes that individuals become increasingly vulnerable to recurrences, such that progressively lower levels of life stress are needed to trigger each subsequent recurrence. The premise elegantly explains the progressive disappearance of major life stress prior to successive recurrences. Lesser stressors begin to substitute for the major life events in provoking onset; in a reciprocal and progressive manner, the severe events become less essential for triggering later recurrences.

Regarding empirical evidence, as indicated above, an abundance of research supports the initial observation of a decreasing relation between severe life events prior to a first onset through successive recurrences (see meta-analysis by Stroud et al. 2008; see also Stroud 2018). These findings, though, are based predominantly on cross-sectional research; very few prospective studies have demonstrated that individuals who are followed to a first onset are more likely to have had a recent severe life event than individuals followed to a recurrence (e.g., Stroud et al. 2011). Crucially, however, all of these findings are predicated on between-person effects, whereas stress sensitization is based upon a within-person effect. Very limited supportive evidence exists for a decline in the presence of severe events over successive episodes within individuals (e.g., Kendler et al. 2000), and alternative explanations for such results have not been ruled out (Monroe & Harkness 2005,

Monroe et al. 2019). Equally crucial, evidence for the unique premise of stress sensitization—that progressively lower degrees of life stress within persons become increasingly more capable of triggering recurrences—does not yet appear to exist (Monroe et al. 2019).

Regarding theoretical considerations, additional limitations and questions recently have been raised about stress sensitization. When one theory dominates, problems can go unnoticed and key questions unasked (Popper 1972). From the outset, the theoretical scope of stress sensitization has been restricted to people who experience major stress before a first onset and who have many recurrences. The theory was developed to focus solely on life stress and recurrent depression. Stress sensitization explicitly excludes first-onset cases who never have any recurrences, and it is silent about first-onset cases without major stress. These two groups are beyond the theory's explanatory purview (Monroe et al. 2019).

A troublesome situation can now be discerned. While stress sensitization theory excludes the 50% or more of first-onset cases without recurrences and first-onset cases without major stress, stress sensitization research has not excluded them from tests of the theory. This realization bears emphasizing: At least 50% of first onsets in the studies reviewed above will never have any recurrences, and thus these individuals are not relevant to tests of stress sensitization. Further, at least 40% of first onsets in the studies reviewed above likely were not preceded by major life events (Monroe et al. 2019, Post 1992), and thus these individuals are also not relevant to tests of stress sensitization. If the association of major life events with recurrences disappears after exclusion of these two substantial groups, stress sensitization would (*a*) no longer explain the original observation that established its credibility and hence (*b*) no longer supply a viable mechanism for any revised observation (see Monroe et al. 2019).

More pointedly for present purposes, by explicitly excluding individuals who never have any recurrences, stress sensitization becomes poorly suited for guiding theory and research on questions about who among the initially depressed will and will not bear depression's greatest burdens. Respectfully, we recognize that these concerns about stress sensitization are not with the theory per se. Rather, they stem from an unwarranted reliance on a single theory to explain virtually everything about depression and its recurrences. Alternative theories are needed. A recent attempt to fill this void is described next.

The Dual Pathway Models

The DPMs were developed to provide an alternative to stress sensitization for understanding depression and its recurrences. A major objective was to establish a theoretical framework for research that could guide discovery of who among the initially depressed will and will not have repeated recurrences over the life course. The basic between-person structure of the theories was founded upon two well-established findings: (*a*) the decreasing association of major life events with successive recurrences, and (*b*) the presence of the two subsets within the overall depressed population, one of which has no (or very few) recurrences, the other of which has many recurrences.

Specifically, this framework posits two related models (DPM-A and DPM-B), each of which describes how depression develops for a nonrecurrent subgroup and for a recurrent subgroup. The pathway to depression for the nonrecurrent subgroup in both DPM-A and DPM-B models is identical. With a relatively low liability to depression, this subgroup requires severe life events, coinciding with other enabling factors at the time (e.g., low social support), to provoke depression onset (Monroe & Simons 1991, Patten 2018). This subgroup is unlikely to have many, if any, recurrences. They are depression capable, not recurrence prone. A perfect storm of a severe event and other ephemerally enabling circumstances may never be encountered again. Recurrences will

be unlikely, arising only in the context of a severe life event. Nonrecurrent cases, too, may have benefited from their depressive experiences. Evolutionary theory proposes that the capability for becoming depressed enhances survival of the immediate threat, potentially steeling the person for survival of future threats (Andrews & Thomson 2009, Gut 1989, Hollon et al. 2021, Keller 2018, Monroe & Harkness 2011, Nesse 2000, Rottenberg et al. 2018). Conceivably, recurrences could become even less likely if severe stress occurs again. The first pathway in DPM-A and DPM-B requires that (*a*) any and all episodes are preceded by a severe life event, (*b*) no, or few, recurrences are experienced over the life course, and (*c*) when relevant, recurrence timing is sporadic with mostly long intermorbid intervals (Anderson et al. 2016, Monroe et al. 2019).

The second pathway of DPM-A and DPM-B depicts two alternative explanations for the origins and lifetime course of depression for the recurrent subgroup. These individuals are recurrence prone. The DPMs propose that members of a recurrent subgroup have an ongoing, pronounced liability to major depression and therefore have episodes repeatedly over time. However, the two DPM models differ in their second pathway regarding the causal conditions for activating the elevated liability for this subgroup eventuating in recurrences. DPM-A posits that the recurrent subgroup is sensitive to stress, such that nonsevere stressors are capable of triggering episodes, even the first one (i.e., onset is not limited to severe events). Based on genetic or familial predisposition (Burcusa & Iacono 2007, Flint & Kendler 2014, Kendler et al. 2001, Monroe et al. 2014b), early adversity (McLaughlin et al. 2010, Nanni et al. 2012), or both factors (Brown et al. 2013), recurrences are triggered mostly by more nonsevere life stress. Therefore, the DPM-A second pathway requires that (*a*) all episodes are triggered by stress (severe or more often nonsevere), (*b*) at least one episode occurs after a nonsevere life event, (*c*) the life course phenotype has many recurrences, and (*d*) intervals between recurrences are relatively consistent and brief (Anderson et al. 2016, Monroe et al. 2019).

The DPM-B second pathway proposes that for the recurrent subgroup, onset of depression is independent of life stress (Monroe et al. 2019). For centuries, a clinically chronicled and frequently severe subset of the depressed population has been described as having episodes appearing out of the blue, unrelated to life stress and/or disproportionate to any discernible stressful circumstances (Jackson 1986). Described under different diagnostic labels, such as "autonomous," "endogenous," and "environmentally insensitive," these presentations are assumed to have biological causes (e.g., Burcusa & Iacono 2007, Healy 2013, Kendler et al. 2001, Lewis 1934, Monroe & Cummins 2017, Monroe & Depue 1991, Monroe & Reid 2009, Parker & Paterson 2014, Shorter 2007, Taylor & Fink 2006, Uher 2008). Therefore, the DPM-B second pathway requires that (*a*) most depressive episodes occur regardless of any form of life stress, (*b*) the life course phenotype has many recurrences, and (*c*) intervals between recurrences are relatively consistent and brief (Monroe et al. 2019).

The two DPM life course pathways of recurrences for the high-liability (recurrence-prone) and low-liability (depression-capable) subgroups are depicted in **Figure 2**. The presence or absence of a severe life event prior to successive episodes distinguishes the two subgroups. The nonrecurrent cases (first pathway) require all episodes to be provoked by severe life events. As a consequence, their proportionate representation within each successive recurrence drops precipitously and progressively, as reflected in the decreasing presence of the mandatory severe life events. In a complementary fashion, the recurrent cases (second pathway) do not require severe events to provoke onset of any episodes. As a consequence, their proportionate representation within each subsequent recurrence rises rapidly and progressively, mirrored by a corresponding drop in the presence of unnecessary severe life events. The collective changing representation of the nonrecurrent and recurrent subgroups over repeated recurrences accounts for the appearance of a decreasing association of severe life events over successive recurrences.

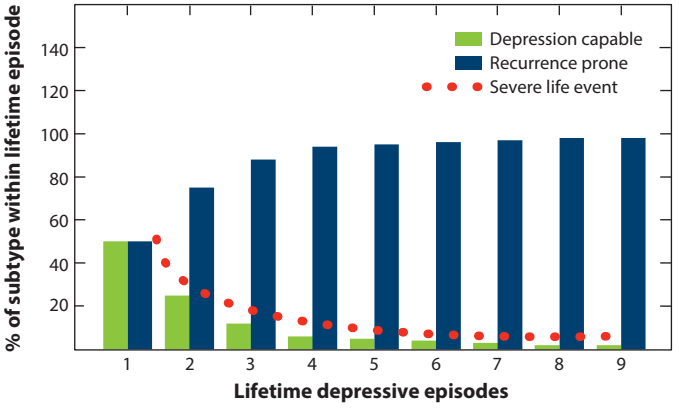

Figure 2

The changing representation of the depression-capable (nonrecurrent) and recurrence-prone (recurrent) subgroups with lifetime depressive episode number as explained by the dual pathway models. The red dotted line represents the decreasing percentage of cases preceded by a severe life event as the depression-capable subtype becomes less common.

General Comparisons Between Stress Sensitization and the Dual Pathway Models

For stress sensitization, theoretical attention is restricted to the neurobiological processes that escalate the liability to depression following life stress, thereby progressively increasing the likelihood of successive recurrences. Consequently, the comparison between people without recurrences and people with recurrences is not a relevant one, and, as such, the theory is incapable of shedding light upon who among the initially depressed will become recurrent. Perhaps the theory could be adapted to redress this limitation, but the singular importance of the nonrecurrent subgroup first needs to be recognized and incorporated into the theoretical and research agenda. Advances such as these possibly could enhance the theory's capability to find early predictors of the recurrent subgroup. But the matter remains open.

The DPMs have been designed specifically to explain the origins of the distinction between depressed persons who have no (or very few) recurrences and those who have very many. Consequently, these models have strong prerequisite credentials for research on early predictors of recurrent depression and the causal mechanisms involved. Given the recency of their introduction (Monroe et al. 2019), few studies as yet have been conducted on the basic precepts and predictions of the models (Anderson et al. 2016). More research on the topic is needed. As detailed next, there is an obvious and potentially decisive initial test for comparing stress sensitization and the DPMs.

Model Comparisons: A Preliminary Yet Potentially Determinative Prediction

Stress sensitization unequivocally specifies that people who become depressed for the first time after a recent major life event are the most vulnerable people to progress to having many recurrences (i.e., to develop recurrent depression). The DPMs clearly specify precisely the opposite: People who become depressed for the first time as a consequence of severe life stress are the least likely to have many recurrences. Are people with a first onset of depression preceded by major life stress more or less likely to have many recurrences—that is, to be those who go on to suffer from recurrent depression?

Whatever outcome emerges, theory will advance, ideally to the eventual benefit of people who suffer recurrences of depression time and again.

CLOSING QUESTIONS AND THOUGHTS

Much still needs to be learned about the recurrent and nonrecurrent subgroups. In the following section, we raise questions and provide additional thoughts for further understanding of the proposed subtype distinction and its implications.

Thoughts on Diagnostic Leniency

Recent classification and diagnostic standards undergird the present-day empirical picture of MDD (i.e., DSM-III through DSM-5; APA 1980, 2000, 2013). Many concerns have been raised about these standards, particularly regarding the types of conditions now formally qualifying as major depression. One of the foremost criticisms has been about a lowering of the diagnostic threshold, which has resulted in the inclusion of distressed but not truly clinically depressed people ("The loss of sadness"; Andrews et al. 2011, Horwitz et al. 2017). Indeed, a major conclusion of a review by de Zwart et al. (2019), that a duration of 2 weeks is too short for the minimum MDE duration criterion, lends strong empirical credibility to this concern. If less clinically severe conditions are assigned false-positive diagnoses of depression (e.g., formerly adjustment disorders, situational stress reactions), how might this alter thinking about the relative proportions of the nonrecurrent and recurrent subgroups?

Conceivably, much of our argument for the nonrecurrent group could be undermined if false-positive diagnoses spuriously inflate the proportion of nonrecurrent cases. For example, a person who has a relatively minor situational distress response might qualify by current standards for an MDE diagnosis but not meet the "spirit" of the clinical syndrome. Such individuals would be relatively low on liability to depression and possibly escape additional episodes for the rest of their lives. They would be one-off diagnostic misfits, empirical anomalies erroneously indexed by overly welcoming diagnostic rules. This scenario would yield more *apparent* nonrecurrent cases, notably countering our emphasis on the often relatively benign course of true major depression, and conceivably undermining the legitimacy of any recurrent/nonrecurrent subtype.

Upon further reflection, though, the implications bear out a more persuasive argument for the opposite interpretation. If present-day standards for defining depression include minor non-MDE conditions, why would an individual inclined to one such reaction be a one-off? Why wouldn't such individuals have many more reactions? With a lowered diagnostic threshold, they would be likely to have more pseudoepisodes and spuriously inflate the recurrent, not the nonrecurrent, subgroup. False-positive first-onset cases would have more false-positive recurrences, thereby overestimating the recurrent subgroup. Overall, any consequences of a lowered diagnostic threshold likely reinforce the premise that most people who become clinically depressed initially do not have many recurrences.

Thoughts on Treatment and Prevention

Research on treatments for depression is voluminous. Acute phase treatments (i.e., promoting response and recovery), and to a lesser extent long-term maintenance treatments (i.e., preventing relapse and recurrence), have received much attention. The bias toward viewing depression as highly recurrent has resulted in precautionary clinical measures (Andrews 2001, Frank et al. 1991). Accordingly, more and more efforts have been directed toward staving off relapses and preventing recurrences following successful treatment.

However, the representation of nonrecurrent cases in the treatment literature is unclear. They may be well represented or underrepresented (overrepresentation seems unlikely). Given the lack of attention to this subgroup, all that can be inferred is that it probably has not been entirely absent (e.g., Hollon et al. 2006, Solomon et al. 2000). Either way, the matter has clear implications for reinterpreting the existing intervention literature and for envisioning how future treatment and prevention practices might be enhanced.

Assuming first that the nonrecurrent cases have been adequately represented in intervention research, what are the clinical implications? If a substantial proportion of first-onset cases never have another episode, how should existing findings be reconsidered? One fact is obvious: Recurrence prevention becomes irrelevant for most people. If the nonrecurrent subgroup could be reliably detected at initial onset, then precious clinical resources and considerable economic costs could be spared and redirected toward the more vulnerable recurrent subgroup. A second fact is that current statistics on acute phase efficacy, maintenance of treatment gains, and prevention of relapses and recurrences are overly optimistic. That is, these data capitalize on the favorable natural course of nonrecurrent cases, thus making treatments appear more beneficial than they actually are. Notably, this applies to control groups as well (e.g., nonrecurrent individuals also would reduce depression to a comparable degree for them).

It is reasonable to speculate that if the nonrecurrent cases could be determined around the time of initial onset, they could be informed of their favorable outlook, alleviating unnecessary concerns about the inevitability of recurrences. If bad things subsequently happened and low mood set in, it would not necessarily signal an impending recurrence and require treatment. Another reasonable speculation is that if the subtype distinction could be made around first onset, efficacy of both acute phase treatments and prevention interventions for recurrent individuals could become better focused, enhanced and personalized according to their susceptibility profile and high liability to recurrence.

Other acute phase treatment implications for nonrecurrent cases are less obvious. Some clinical matters, though, deserve to be weighed. First, if nonrecurrent cases are more likely than recurrent cases to recover relatively quickly and without formal assistance (e.g., "spontaneous" remissions), is treatment necessary for them? Both empirically supported psychotherapy and antidepressant medications require weeks to achieve their effects; treatment might minimally shorten episode duration for the nonrecurrent subgroup. (This would be especially so if treatment seeking is delayed for first-episode cases, perhaps due to life stress; e.g., Ginsberg & Brown 1982; cf. Monroe et al. 1991). Further, even under optimal treatment conditions, recovery rates remain modest (Ormel et al. 2022). Whether these modest success rates exceed those for the natural course of the nonrecurrent subgroup is an empirical question. Fewer days with depression, though, would still seem to be a therapeutic success and a compassionate goal. One is tempted to declare "sooner better than later," "no harm done," and "be safe, not sorry."

But this raises a second question about the propriety of acute phase treatment for the nonrecurrent subgroup. Many well-intended and initially promising psychological interventions have proven ultimately to have few beneficial effects, and sometimes deleterious consequences (Lilienfeld 2007). Could psychotherapy or antidepressant medications be of no use or even harmful for the nonrecurrent subgroup? Antidepressant medications have many side effects, and tapering medications following successful treatment often can be difficult (e.g., withdrawal symptoms or oppositional tolerance can mimic recurrence symptoms; Andrews et al. 2011, Fava 2020, Ormel et al. 2022). Pharmacological and psychological treatments also might reduce self-help activities and the patient's sense of self-efficacy (Haslam 2016, Meadows et al. 2019, Ormel et al. 2022). Lastly, evolutionary theory provides a further cautionary note. Could active treatments for nonrecurrent individuals impede natural adaptions? Might they hamper learning coping and

problem-solving abilities as well as one's sense of agency to overcome her or his depression, perhaps iatrogenically rendering such individuals vulnerable to recurrences (Hollon 2020)? These matters require careful consideration regarding treatments for the nonrecurrent subgroup.

Second, assuming that the nonrecurrent cases have not been adequately represented in intervention research, what are the clinical implications? Many simply are the opposite of those assuming adequate representation (e.g., efficacy data for existing treatments will be more accurate). But one point stands out: Efficacy of treatments for the nonrecurrent subgroup would be unknown. Once again, this would provide a caveat about treating nonrecurrent individuals with interventions that might lack demonstrated support for their condition.

All in all, thinking through treatment considerations in light of the recurrent/nonrecurrent subtype compels further recognition of how little is known about the nonrecurrent subgroup and how important it is to better understand the implications for current thinking about major depression.

Reevaluating Candidate Risk Indicators

As reviewed previously, many studies have investigated general predictors of recurrence. Some support has been garnered for genetic factors, family history of depression, early age of onset, early adversity, residual symptoms after recovery, and neuroticism (albeit not always consistent; see Buckman et al. 2018, Burcusa & Iacono 2007, Hardeveld et al. 2010). Intriguingly too, women are more likely than men to become depressed initially but may not be more likely to have recurrences (Kessler et al. 1993). But none of these candidate risk indicators has risen to the level of being clinically useful or scientifically compelling. How does recognition of the recurrent/nonrecurrent subtype possibly improve understanding and the potential of general predictors?

Prognostic "signals" from research on recurrences would have been affected by variable proportions of recurrent and nonrecurrent cases from one study to the next. This again may explain inconsistent findings (Buckman et al. 2018). More pointedly, it indicates that risk factors are moderated by subgroup. Rather than inconsistently or weakly predicting recurrences in general, the predictors could be expected to distinguish between the two subgroups more reliably and robustly (perhaps especially so when evaluated cumulatively; Hardeveld et al. 2013). For example, most predictors have the common theme of an ongoing elevated susceptibility to depression (i.e., genetic factors, family history of depression, early age of onset, early adversity, and neuroticism). They are markers for a high probability of becoming depressed repeatedly over the life course. Their predictive strength should be enhanced to help distinguish the recurrent from the nonrecurrent subgroup.

What about gender? Since overall women are more likely to become depressed but are not thought more likely to become recurrent, women should be overrepresented within the nonrecurrent subgroup (e.g., van Loo et al. 2018). This would be good news prognostically for women, as their relative likelihood of having another episode would be reduced. (Interestingly, this also implies that the gender differences in depression could be primarily for the nonrecurrent subgroup.) Unfortunately for men this would be bad news, as those depressed for the first time would be more likely to become recurrent. Parity of prognosis would equalize with more recurrences.

Finally, residual symptoms are considered to be among the most robust predictors of recurrences (Buckman et al. 2018, Hardeveld et al. 2010). Their presence would be expected to signify the recurrent subgroup. Although residual symptoms might represent just another general indicator of liability to recurrences, they also could be theoretically informative. According to stress sensitization, after recovery from an initial episode provoked by major stress, the accruing vulnerability could be manifested as postrecovery residual symptoms (which would predict a greater

likelihood of recurrences). In contrast, according to the DPMs, an initial depressive episode provoked by a severe event predicts the opposite, a more complete and stable postrecovery clinical picture (which would predict a lower likelihood of recurrences). Do people who experience a first onset provoked by severe stress have better or worse postrecovery symptomatic functioning and, ultimately, better or worse chances of many recurrences? We close with another intriguing opportunity to directly compare the two theoretical systems for understanding recurrences and for learning more about who among the initially depressed will become recurrent.

SUMMARY POINTS

1. Among people who develop major depression for the first time, some will have recurrences over the rest of their lives, whereas most will likely never experience a single recurrence.
2. Presently, it cannot be reliably forecasted at the time of initial depression onset who will and who will not have few or many lifetime recurrences.
3. The ability to predict lifelong recurrences among those who become depressed for the first time could transform advances for alleviating the individual and global burdens of major depression.
4. Many established beliefs about major depression require reevaluation in light of recurrent and nonrecurrent subsets within the population of depressed individuals.
5. Conceptual biases, definitional dead ends, faulty research designs, and the lack of descriptive data begin to explain failures to discover early prognostic indicators for the differing life course trajectories of the recurrent and nonrecurrent subgroups.
6. Two competing theories about the causes of recurrences, based on the presence or absence of severe life events, hold promise for advancing understanding of who among the initially depressed will and will not be burdened by repeated recurrences over the life course.

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