Recurrence in Major Depression: A Conceptual Analysis

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Theory and research on major depression have increasingly assumed a recurrent chronic disease model. Yet not all people who become depressed suffer recurrences, suggesting that depression is also an acute, time-limited condition. However, few if any risk indicators are available to forecast which of the initially depressed will or will not recur. This diagnostic impasse may be a result of problems in conceptualizing the nature of recurrence in depression. In the current paper we first provide a conceptual analysis of the assumptions and theoretical systems that presently structure thinking on recurrence. This analysis reveals key concerns that have distorted views about the long-term course of depression. Second, as a consequence of these theoretical problems we suggest that investigative attention has been biased toward recurrent forms of depression and away from acute, time-limited conditions. Third, an analysis of how these theoretical problems have influenced research practices reveals that an essential comparison group has been omitted from research on recurrence: people with a single lifetime episode of depression. We suggest that this startling omission may explain why so few predictors of recurrence have as yet been found. Finally, we examine the reasons for this oversight, document the validity of depression as an acute, time-limited disorder, and provide suggestions for future research with the goal of discovering early risk indicators for recurrent depression.

Keywords: major depression, risk factors, recurrence, nonrecurrence, chronicity

Major depressive disorder (MDD) is one of the most common, debilitating, and deadly psychiatric conditions. The projected lifetime risk is approximately 23% in the United States (Kessler & Wang, 2009), and depression is expected to be the second leading cause of disability worldwide by 2020 (Murray & Lopez, 1996). The costs to society, too, are enormous, estimated in excess of $36 billion annually in the United States alone (Kessler & Wang, 2009). Long recognized as the most prevalent psychological condition associated with suicide (Berman, 2009), depression more recently has been linked to the development of other life-threatening medical conditions (e.g., coronary heart disease, Goldston & Baillie, 2008; Wulsin & Singal, 2003; diabetes, Knol et al., 2006; Mezuk, Eaton, Albrecht, & Golden, 2008). From both individual and public health perspectives, MDD poses a problem of major significance and pressing importance.

One of the most crippling and devastating aspects of depression is its recurrent nature. According to present estimates approximately 60% of people who develop a first lifetime episode of MDD will incur a second episode, 70% of those with a second will suffer a third, and 90% of those with three or more episodes will experience further, often many more, recurrences (American Psychiatric Association, 2000; Solomon et al., 2000). Figure 1 portrays these risk estimates as a function of the number of lifetime episodes experienced. Every recurrence also carries a 10–20% risk of becoming unremitting and chronic, along with a heightened risk for suicide, both of which further compound the serious complications and lethal consequences associated with the depression (Lee, 2003). Data such as these emerging over recent years have led the field to view depression increasingly as a chronically recurring medical condition, requiring prolonged treatment over time (e.g., Andrews, 2001; Keller, 2003; Surtees & Barkley, 1994).

Complementing these societal and human mandates for focusing on recurrence of depression are compelling theoretical and scientific reasons (Belsher & Costello, 1988). Many studies have found that predictors of first lifetime episodes of depression differ from predictors of recurrences. For example, although gender is strongly associated with developing depression initially, it is believed to be unrelated to recurrences (Burcusa & Iacono, 2007; Coryell, Endicott, & Keller, 1991; Lewinsohn, Allen, Seeley, & Gotlib, 1999). Research on life stress, too, finds that the relationship between major life events and depression is strongest for initial lifetime episodes and lessens over repeated episodes (Kendler, Thornton, & Gardner, 2000; Monroe & Harkness, 2005). Finally, as indicated in Figure 1, each new occurrence of depression appears to be associated with increasing risk of yet another episode (Mueller et al., 1999; Solomon et al., 2000). Collectively, these studies imply differences in the causal mechanisms involved with a first onset as opposed to a recurrence, which again reinforces the potential utility of research that focuses primarily on the nature of recurrence.
Establishing predictors of recurrence early in the lifetime course of depression could transform basic and clinical research, potentially leading to breakthroughs in understanding and preventing recurrences. Individuals at high risk for recurrence could be compared with individuals at low risk, permitting more powerful investigations of the genetic, endophenotypic, biological, psychological, and social correlates and contributors to recurrence. To illuminate the etiologically relevant predictors of recurrence, though, it is especially important to study recurrent-prone individuals prior to developing multiple episodes. Early differences between those who go on to recurrences versus those who do not are thereby likely to be of causal relevance (as opposed to being concomitants or consequences of already having experienced multiple episodes or treatments for depression). Intervention research, too, could be dramatically improved. For example, characterization of a high-risk recurrence group would allow for the development of intervention procedures specifically designed to remediate established recurrence vulnerabilities.

The primary obstacle for theory and research on these issues is that we currently possess few, if any, clinically or scientifically useful predictors for who, once initially depressed, will or will not eventually recur. We suggest that the estimate that 60% of individuals with an initial depressive episode go on to suffer recurrences has led the field to underplay the corollary statistic—that 40% or more of those with an initial depressive episode do not recur. Rather, these latter individuals experience but a single lifetime episode of depression. This is a very significant number from clinical and public health perspectives, and it represents a singular group theoretically.

These data on recurrence highlight a central paradox about depression: At least phenotypically, the disorder can be both an acute, time-limited condition and a chronically recurring, lifelong condition. A key question concerns what distinguishes individuals who incur a first lifetime episode and never experience another depression from those who experience recurrences. Our goal is to undertake a systematic evaluation of the concept of recurrence and its implications for research on depression. We believe that this detailed theoretical analysis will help to lay the foundations for research with great potential for discovering early indicators of recurrence risk.

**Overview**

Our primary objective is to evaluate contemporary concepts that structure thinking and research on recurrence and nonrecurrence of major depression. We do not address specific theories or models of recurrence (e.g., kindling or genetic models; see Burcusa & Iacono, 2007; Monroe & Harkness, 2005; Monroe, 2010), as these topics will require separate treatment in light of the present analysis. Our companion objective is to provide insights into how depressed individuals prone to developing recurrences may be identified and investigated very early in the life course of the disorder.

After clarifying terminology, we address three interrelated issues that undergird the theoretical problems with current thinking on recurrence and help to explain the present inability to predict which depressed individuals will suffer recurrences and which will not. First, we systematically evaluate how the construct of recurrence has been fundamentally conceived and defined, thereby revealing key problems that have distorted thinking about recurrence and the long-term course of depression. Second, we evaluate how these conceptual problems have prejudiced research practices, resulting in studies poorly designed to discover early risk indicators of recurrence. Third, we establish how theory, research design, and investigative practice have inadvertently omitted information on acute forms of depression (i.e., people who do not recur). This oversight has led to biased estimates of recurrence and premature pessimism about finding early risk indicators for recurrence. Finally, we discuss directions for future research that can enhance...
understanding on the nature of depression, its recurrences, and overall morbidity over the life course.

**Preliminary Considerations: Terminological Confusions**

The core vocabulary in research on recurrence has often been confused by imprecision in the use of related ideas and terms. The general term **recurrence** designates a depressed person who, after full recovery from the depressive episode, becomes clinically depressed again at a later point in time (see Table 1). Note that this could denote any lifetime recurrence of MDD (e.g., a second or fifth lifetime episode). We use the term **nonrecurrence** to designate a previously depressed person who, after recovery from an episode, never becomes diagnostically depressed again. Note, too, that someone can become a nonrecurrence after, for instance, a first or a fifth lifetime episode. Whatever point in the lifetime course of depression at which the individual ceases to experience new episodes of MDD is the point at which he or she becomes a nonrecurrence. It is useful to keep in mind that recurrence and nonrecurrence represent generic labels that are nonspecific with regard to prior history of depressive episodes.

These general terms are to be contrasted with more specific terms that provide greater information about any particular instance of a recurrence or nonrecurrence. For example, a single lifetime episode of depression (SLED) is a special case of a nonrecurrence. It represents a person who does not recur following a first lifetime onset. Thus individuals with a SLED have only one episode of MDD over the entire life course. Nonrecurrence often has been confused with a SLED; however, as noted above, the generic term **nonrecurrence** includes those with a SLED as well as those with more than one prior lifetime episode who, at some point, do not incur another episode. Similarly, people with a SLED often have been viewed interchangeably with people experiencing a first lifetime episode of depression (FLED). However, people with a SLED represent a subset of people with a FLED, as some people with a FLED will eventually recur (and consequently will not be people with a SLED) and some will not recur (and consequently will be people with a SLED). Hence, people with a FLED represent an indeterminate mixture of people with a SLED and people with future recurrence. As we see later, confusing people with a FLED and people with a SLED has created many problems for research on recurrence. We employ the terms **first lifetime episode of depression (FLED)** and **single lifetime episode of depression** (SLED) to designate these specific groupings, reserving **recurrence and nonrecurrence** for the more general terminology.

Additional confusion can arise in the context of studies that follow patients from their index episode to their first prospective recurrence (e.g., Solomon et al., 2000). The **index episode** is another generic term that has no specific meaning with regard to prior number of lifetime episodes. For some participants the index

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**Table 1**

**Terminology Commonly Used in Research on Recurrence of Depression**

<table>
<thead>
<tr>
<th>Term</th>
<th>General definition</th>
<th>Confusion to avoid</th>
</tr>
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<tbody>
<tr>
<td>Recurrence</td>
<td>A major depressive episode (MDE) developed by a person who has experienced and recovered from at least 1 prior MDE.</td>
<td>A generic term to refer to any recurrence of MDE in the person’s life. The recurrence could be a first recurrence or a fifth. Not to be confused with a first lifetime recurrence.</td>
</tr>
<tr>
<td>Nonrecurrence</td>
<td>After a person develops at least one MDE and recovers, the person never experiences another MDE over the life course.</td>
<td>A generic term to refer to any nonrecurrence of MDE in the person’s life. The person may never experience another MDE after a first lifetime episode or, for example, a fifth lifetime episode. Not to be confused with a first lifetime episode or a single lifetime episode (SLED).</td>
</tr>
<tr>
<td>First lifetime episode of depression (FLED)</td>
<td>The first MDE in the person’s life.</td>
<td>The first lifetime MDE may not be the only lifetime episode of MDE, as subsequent recurrences may occur. Not to be confused with single lifetime episode of depression (SLED).</td>
</tr>
<tr>
<td>Single lifetime episode of depression (SLED)</td>
<td>The only MDE in the person’s life.</td>
<td>The only lifetime episode of MDE means that there is never a recurrence. Not to be confused with first lifetime episode of depression (FLED).</td>
</tr>
<tr>
<td>Index episode</td>
<td>The current episode of MDE.</td>
<td>A generic term to refer to any MDE that brought the person into the research protocol. The episode in the life course of the person is arbitrary; it could be a FLED, a SLED, a first recurrence, or a fifth recurrence. Not to be confused with more specific terms of FLED or SLED.</td>
</tr>
<tr>
<td>Recurrent depression</td>
<td>A person who has several lifetime MDEs.</td>
<td>By current standards, this is defined by a minimum of 2 lifetime episodes of MDE. Not to be confused with a generic recurrence.</td>
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</tbody>
</table>
episode may be a first lifetime episode, but for others it may be the eighth or the 15th. Further, the sampling of the index episode within the life course of the particular participant probably is arbitrary. The study could be indexing a first lifetime episode for the participant, but if the study happened to take place 20 years hence, the same participant could be in a 10th lifetime episode.

With respect to a first prospective recurrence, parallel confusions can arise. Again, a first prospective recurrence could be the very first or the 12th recurrence, depending on the chance timing of the study. Overall, misunderstandings frequently occur if it is not recognized that the timing of an index episode is arbitrary in the life course of the participant. As a generic term, the index episode could reflect a FLED, a SLED, a final lifetime episode, or simply one recurrence among many previous and many future episodes.

A final general source of confusion stems from differences across studies in what actually constitutes a recurrence. For example, in the landmark Collaborative Depression Study (CDS), recurrence was operationalized as a new episode of MDD in one report (Solomon et al., 2000), as a new episode of major or minor depression in another report (Lavori et al., 1994), and as an “episode of affective disorder” in yet a further report (Mueller et al., 1999). In the last study, 22% of the designated recurrences were not episodes of MDD but rather were episodes of schizoaffective disorder, hypomania, and mania. These different meanings of recurrence are easily overlooked and can be indiscriminately equated across investigations. The quest to capture accurate rates of recurrence and to find early predictors of recurrence obviously will be compromised when different clinical phenomena are included within the definitional boundaries of recurrence.

### On Defining Recurrence: Assumptions, Concepts, and Practices

Recognizing serious inconsistencies and problems in defining change points in the clinical course of depression, the MacArthur Foundation Research Network on the Psychobiology of Depression convened a task force in 1988. Based on these deliberations, a thoughtful review and precedent-setting article was published that proposed a conceptual system for defining and operationalizing recurrence and related constructs (Frank et al., 1991). Table 2 presents the conceptual definitions and current operational examples of these terms, along with the key underlying assumptions. Frank et al. (1991) were firm about the provisional nature of the proposed conceptual scheme and “enthusiastically invite others to challenge [their] tentative suggestions with alternative conceptualizations and for empirically derived criteria” (p. 855).

Despite the entreaties of Frank et al. (1991), there has been almost no research bearing upon these definitions and their respective assumptions. Yet it is this system that has guided research on recurrence for more than two decades and that has been reaffirmed by recent consensus conferences on mood disorders (Rush et al., 2006; Tohen et al., 2009). Indeed, there have been roughly as many consensus reports and commentaries (Fava, Ruini, & Be- laise, 2007; Kupfer & Frank, 2001; Rush et al., 2006; Segal, Pearson, & Thase, 2003; Tohen et al., 2009) as there have been empirical studies (Hawley, Gale, Survakumar, & Hertfordshire Neuroscience Research Group, 2002; O’Leary, Hickey, Lagerdom, & Webb, 2010; Philipp & Fickinger, 1993; Reimherr et al., 1998;

### Table 2

**The MacArthur Report System for Conceptualizing and Defining the Clinical Course of Major Depression**

<table>
<thead>
<tr>
<th>Term</th>
<th>Conceptual definitions</th>
<th>Operational definitions</th>
<th>Endpoint</th>
<th>Critical assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>Following onset of a major depressive episode (MDE), an initial, relatively brief period of symptom improvement during which there is a virtual absence of depressive symptoms.</td>
<td>Current recommendations are for 3 consecutive weeks of sustained improvement to initiate remission; if maintained for 4 months, remission becomes recovery.</td>
<td>Relapse or recovery</td>
<td>The underlying neurobiology of the index episode remains active, and the person is vulnerable to falling back into the index MDE.</td>
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<tr>
<td>Recovery</td>
<td>Following a sufficient period of sustained remission, a period of symptom improvement such that continued well-being is expected and an MDE is unlikely to occur in the near future.</td>
<td>Current recommendations are for sustained improvement for 4 months of remission. Symptomatic “roughening” or subsyndromal symptoms not meeting criteria for MDE are permitted.</td>
<td>Recurrence</td>
<td>The neurobiology of the index episode is resolved; relapse is no longer possible. Recovery is presumed from the prior episode of MDE and not from the illness (i.e., the underlying vulnerability to future episodes of MDE remains).</td>
</tr>
<tr>
<td>Relapse</td>
<td>A return to the index MDE following the onset of remission but before fulfilling the criteria for recovery.</td>
<td>Current recommendations are a return of symptoms meeting criteria for MDE after 3 weeks of improvement but before completing 4 months of sustained improvement.</td>
<td>Remission</td>
<td>Diffs from recurrence with respect to time since remission and assumed differences in underlying vulnerability.</td>
</tr>
<tr>
<td>Recurrence</td>
<td>The development of a new episode of MDE after completing remission and attaining recovery.</td>
<td>Current recommendations are for a return to MDE status after 4 months of symptom improvement (i.e., full remission). Symptomatic “roughening” or subsyndromal symptoms not meeting criteria for MDE are permitted.</td>
<td>Remission</td>
<td>Any new occurrence of MDE is conceptualized as a recurrence as opposed to a new MDE or a different illness.</td>
</tr>
</tbody>
</table>
Riso et al., 1997). Most important, there has been no critical analysis of the proposed conceptual system, its assumptions, and its implications. This means that for two decades, research on recurrence has been guided largely by a set of ideas and operationalizations that, although important at the time and useful for many purposes, has been accepted mostly on faith, with minimal evidence, and essentially without discussion.

Defining Recurrence: Prerequisite Criteria

As stated above, a recurrence involves the reemergence of clinical depression after full recovery from a prior depressive episode. This definition appears straightforward; however, in practice, determining when an individual has suffered a recurrence becomes an unexpectedly complicated endeavor. This is because recurrence is fundamentally intertwined within a broader system of ideas designed to explain the clinical course of depression (see Table 2). In an important sense, recurrence represents the tip of the conceptual iceberg and can be evaluated only within the larger theoretical system in which it is embedded.

A person cannot have a recurrence until he or she has had an episode of depression and has recovered from that episode. The definitional desiderata for establishing recovery involve primarily (a) the degree and (b) the duration of symptomatic improvement. According to the MacArthur criteria, individuals who meet the guidelines for symptomatic improvement (see Table 2) enter a transition period of remission, and during remission any reemergence of full criterial symptoms is deemed a relapse. Relapse is not the same as recurrence, as it is based on the premise that, during remission from an episode of MDD, a reemergence of MDD signifies "the return of the symptoms of a still ongoing but symptomatically suppressed episode" (Frank et al., 1991, p. 853). In contrast, after a sustained period of remission, the episode is considered to be over, and recovery is formally declared. Any reemergence of MDD thereafter is designated a recurrence, which is thought to represent a new instance of depression.

Based on this system of ideas, relapse is assumed to arise out of the labile pathophysiologic aftermath of the recent episode, whereas recurrence is assumed to arise out of the more enduring psychobiologic liability for depression. The nature of these two mechanisms remains unknown, but presumably they differ in critical ways. To date, however, the only means of distinguishing between relapse and recurrence has been defined arbitrarily in terms of the degree and duration of symptomatic improvement. Therefore, the discriminant validity of these two constructs rests on shifting sands of decisions about the criteria for distinguishing between remission and recovery. This is important because varying these criteria can result in very different numbers of people defined as suffering from brand-new recurrent episodes versus relapses of the same episode.

For example, in a report by Philipp and Fickinger (1993) the MDD episode duration for a sample of psychiatric inpatients was evaluated when the criteria for defining the end of the episode were 5, 4, 3, 2, or 1 symptoms of MDD. The more stringent the criteria, the longer the median episode length was for the sample (i.e., time to recovery). There was a 6.6-fold difference in median episode length between the criteria of fewer than five symptoms (4.0 weeks) versus one symptom (26.5 weeks). Similarly, alterations in the duration requirement for recovery can produce up to fourfold differences in the episode length (see Furukawa et al., 2008; O’Leary et al., 2010). The general point is that different criteria for defining remission versus recovery produce very different groups of individuals becoming eligible for recurrence.

More concretely, the parameters required for recovery can be varied to create the appearance of quite different clinical pictures based on identical clinical data. For example, in Figure 2 two identical clinical profiles are presented, differing only in the degree of symptomatic improvement required for defining recurrence (i.e., for this example, duration of symptomatic improvement is held constant). At the top of Figure 2 is a liberal symptom criterion, with the threshold for defining recovery representing minimum symptom improvement. This leads very quickly to a large number of spurious recurrences (i.e., false positives), cases where minor shifts in symptomatic functioning cross the diagnostic threshold and create the illusion of four recurrences over time. These improved but still significantly symptomatic cases likely drift across the diagnostic boundary of MDD, rather than shift in a more extreme psychobiologic sense indicative of a true recurrence (i.e., a new episode). In contrast, the bottom of Figure 2 depicts a conservative symptom criterion, with the threshold for defining recovery being a very stringent degree of symptomatic improvement. In this latter profile, only one recurrence would be declared over an extended period of time. The complementary concern, of course, is that such a definitional system is insensitive for detecting true recurrences (i.e., false negatives).

In Figure 3 three other clinical profiles are presented, in this illustration focusing on the consequences of varying the duration requirement for symptomatic improvement (i.e., for this example, the degree of symptom improvement is held constant). At the top of the figure a liberal duration requirement is depicted, wherein brief symptomatic improvement results in three recurrence declarations. When the duration requirement is increased, the middle and bottom profiles become progressively more conservative and yield proportionately fewer recurrence declarations. The clinical profiles in Figures 2 and 3 graphically reveal the delicate balance and tensions between the required degree and duration of symptomatic improvement and, most important, their implications for research on recurrence.

At one extreme, recurrences become lost in a sea of chronically afflicted individuals whose symptoms merely wax and wane. At the other extreme, recurrences vanish from view as they are erroneously eliminated from the protocol over time. Either of these two extremes produces biased findings that impede the ability to...
provide accurate recurrence estimates and to detect early indicators of recurrence. How to best locate the construct of recurrence within the parameters of these clinical preconditions represents a crucial conceptual question, one that requires more detailed analyses of the assumptions involving recurrence. We turn to these topics next.

Defining Recurrence: Reconsidering Chronic Depression

Regardless of decisions about the most appropriate criteria for establishing a recurrence versus a relapse, a significant minority of individuals with depression fails to achieve symptomatic improvement, even after very prolonged periods of time. Chronic MDD is defined by the DSM–IV as a major depressive episode that lasts at least 2 years, although many individuals with chronic depression report a much longer course of illness (Klein, 2010). Because in most studies people with chronic depression typically do not remit in time to become candidates for recurrence, chronic depression can appear to be a separate psychiatric entity (see, e.g., Hollon et al., 2006).

Yet in many cases this appearance could be an artifact of the arbitrary timing of the index episode of MDD in the life course of the individual. For instance, it is estimated that each new recurrent episode of depression entails a 10–20% risk for developing into a chronic depression (Lee, 2003). Further, most individuals with chronic depression eventually recover, and at least some go on to experience subsequent recurrences (e.g., Lavord et al., 1994; Solomon et al., 2000). Enlarging the time frame of clinical observation to encompass the lifetime course of depressed persons suggests that recurrent and chronic depression can alternate over time for many individuals and, as such, could represent an alternative expression of the same underlying liability. Therefore, parsing chronic and recurrent depression into separate categories based on any one arbitrary point in time or, worse, excluding chronic depression entirely from studies on depression’s recurrence may reduce the power to detect predictors of recurrence and underestimate the overall morbidity of depression over the life course.3

Reconsidering Relapse: Evidential Arguments

These cautionary comments on strictly separating recurrent and chronic depression based on one arbitrary point in time point can be extended to separating recurrence and relapse. Although the distinction between relapse and recurrence is a critical one that has become part of established recommendations for research on both unipolar and bipolar disorders (see Rush et al., 2006; Tohen et al., 2009), only a few studies have addressed the empirical basis for the distinction (Furukawa et al., 2008; O’Leary et al., 2010; Philipp & Fickinger, 1993). These studies generally reported that the risk for becoming depressed again is greatest immediately following improvement and progressively diminishes thereafter (Boland & Keller, 2009; O’Leary et al., 2010). Overall, “the great majority of relapses occur within the first 4 months of the year following remission” (Rush et al., 2006, p. 1847; see also Reimherr et al., 1998).

However, as yet there is little evidence supporting any qualitative distinction between relapse and recurrence. In fact, without other evidence (e.g., a “point of rarity” or distinct changes in survival curves; see Frank et al., 1991; Rush et al., 2006), these findings can be most parsimoniously interpreted as evidence against any qualitative distinction. Simply stated, the longer the time requirement for sustained improvement and recovery, the lower the likelihood of a new episode of depression emerging.

Through again enlarging the clinical time frame to encompass the lifetime course of the depressed person, perspectives might be gained for evaluating whether relapse and recurrence should be distinguished. For example, individuals with multiple recurrences commonly experience relapses following some episodes (Kupfer & Frank, 1987). Further, a greater number of prior depressive episodes also predicts subsequent relapse (see Boland & Keller, 2009; Limosin et al., 2004; cf. Parker, Holmes, & Manicavasagar, 1986). Thus, an individual may relapse at one point in time, whereas at another point in time the same individual may recur. In reasoning parallel to that described above with regard to chronic depression, over the broader sweep of time, relapse and recurrence

3 It is important to point out that with these examples we focus upon people who meet criteria for chronic depression, yet who also eventually recover from the episode. This is not to minimize people with other chronic depressive conditions who do not recover over exceedingly prolonged periods of time (Klein, 2010). Our argument is not against the validity of chronic depression but is for considering a portion of what is currently viewed as chronic to be considered from a broader life course perspective as possibly also being recurrent.
may represent alternative phenotypic expressions of a common underlying liability. By excluding individuals who relapse from studies on recurrence, research practices may inadvertently but systematically eliminate a highly vulnerable group that could be informative for risk indicators of recurrence and for a broader understanding of the morbidities associated with depression over the life course.

Reconsidering Relapse: Conceptual Arguments

Frank et al. (1991) suggested that recovery “is used to designate recovery from the episode, not from the illness per se” (p. 853). This basic premise has been adopted widely and is reiterated verbatim in recent major consensus reports on mood disorders (see Rush et al., 2006; Tohen et al., 2009). Recovery, though, is a silent but sovereign construct that operates behind the scenes within this interrelated system of assumptions, ideas, and definitions that currently structure thinking about relapse and recurrence (see Table 2). A theoretical examination of this particular assumption reveals tensions between the constructs of relapse and recurrence, which in turn portend problems for research on recurrence.

What does it mean to recover from the episode of depression but not from the illness of depression? From the perspective of a chronic disease model, each new instance of depression is thought to arise from an enduring underlying liability (i.e., recovery from the episode but not from the illness). In essence, this means that after initially contracting the illness, the person is never considered to be free, or cured, of the underlying condition. Relapse and recurrence appear very similar from this vantage point, as they arise from the same ongoing vulnerability. Consequently, there does not appear to be a need for two separate constructs.

In contrast, from an acute disease perspective (i.e., one can recover from the illness), the idea of a relapse appears to make theoretical sense but the independent idea of a recurrence less so. For example, virtually all people have contracted a cold or the flu. These afflicted individuals may get a bit better, then backslide, for which “relapse” appears to be a suitable descriptor. But after these afflicted people recover and incur the disease again at a later point in time, the new episode typically is not viewed as a recurrence. It is referred to as a new illness. Consequently, from an acute disease perspective, recurrence appears difficult to locate in a separate conceptual space and may be most usefully considered simply to represent a new instance of the illness.

From a chronic disease perspective, then, relapse and recurrence are difficult to distinguish conceptually, as they appear to be predicated upon the same underlying pathology. From an acute disease perspective, the need for two separate constructs also is questionable; relapse may represent a useful term, but recurrence may be an unwarranted additional term. From either perspective, the need for two separate constructs appears to be potentially misleading and certainly not theoretically parsimonious.

Another problem with the assumption of “recovery from the episode, not from the illness per se” is that it directly clashes with depression as an acute, time-limited condition. However, the evidence in support of both the acute and recurrent disease models for depression is prima facie: Of people who become depressed, approximately half never do so again and approximately half do (Eaton et al., 2008). In other words, if at least half of those initially

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4 At the time, the field was just beginning to recognize how disabling depression could be over the life course and was overcoming the prior biases favoring depression as solely an acute clinical entity. By incorporating both acute and chronic components in their conceptual system, Frank et al. (1991) were attempting to bring the chronic and recurrent components of depression more concretely into the theoretical and investigative arena.
depressed never experience another instance of the disorder, any assumption about an enduring illness becomes quite questionable. We further examine the problematic implications of this assumption for research on recurrence next.

Reconsidering Recurrence and the Heterogeneity of Depression

The assumption that recovery designates recovery from the episode, not from the illness per se, mandates that any future episode is de facto a recurrence of the same underlying disease. However, there are several reasons to suspect that not all instances of depression in a person’s life are necessarily due to the same etiology. Depression currently is commonly understood to represent a heterogeneous class of psychological conditions, in terms both of phenotypic expression and of etiology (Drevets, 2001; Kendler, Thornton, & Gardner, 2001; Thase, 2009; Uber, 2008; van Praag, de Kloet, & van Os, 2004; Winokur, 1997). Although it is common to think of heterogeneity in terms of different disorders for different individuals, one person could incur two etiologically distinct forms of depression over the life course. Research on recurrence of depression has proceeded as if all recurrences reflect a common underlying illness or process that characterizes a single category of disease. Yet someone could suffer from two or more instances of “generic” DSM–IV MDD over the life course, and those episodes would not necessarily be attributable to the same causal factors (see also Belsher & Costello, 1988).

Consider a person who becomes depressed at age 20 for the first time, following a devastating romantic loss. The clinical presentation includes symptoms of depressed mood, psychomotor agitation, crying, hopelessness, and feelings of worthlessness. Suppose the same individual becomes depressed for a second time at age 78, in the context of little or no environmental adversity but with white matter hyperintensities appearing on a CT scan. The syndromal presentation for this second episode includes diminished pleasure, cognitive impairments, psychomotor retardation, and guilt. Most investigators probably would not consider this latter episode to reflect the spirit and substance of a recurrence.

If the same individual can experience etiologically distinct manifestations of depression over the life course, then the sweeping assumption that all new manifestations represent recurrences of the same illness impedes the quest to determine, early on, which individuals are likely to have a recurrent course to their depression and which are not (Belsher & Costello, 1988). This is because if all instances of subsequent MDD are preordained as recurrences, yet other sporadic or alternative etiologic forms of MDD exist, these latter instances automatically and erroneously are designated as recurrences. In actuality, though, these latter episodes represent false-positive recurrences, and these cases would dilute the pool of people who experience true recurrences. This situation compromises early detection of a recurrent subtype of depression, with the problem being of greater or lesser degree depending upon the prevalence of alternative subtypes of depression in any particular study.

At the current stage of knowledge, it is unknown whether some people who become depressed for a first time recover from the episode only or whether at least some people fully recover from the condition with which they originally were afflicted. Not all first lifetime depressed individuals will have another episode, so it seems at least equally plausible that some people can recover from the episode and from the illness. It is also plausible that some individuals who have a first lifetime episode and recover may incur another, etiologically distinct form of depression sometime over the life course; such later instances of depression may be best considered to be new forms of the illness, not recurrences of the same illness. Present approaches to conceptualizing recurrence need to accommodate the fact that not all incident cases of depression recur and the possibility that different subtypes of depression can arise over the life course.

Defining Recurrent Depression

Two critical features of recurrent depression require clarification. First, what number of depressive episodes best establishes recurrent depression? Current conventions assume the critical divide is between a first lifetime episode and a second and therefore define recurrent depression as two or more lifetime episodes of MDD (American Psychiatric Association, 2000; Hollon et al., 2006). However, many theorists and investigators consider the defining line of two lifetime episodes for recurrent depression to be too permissive, to lump a heterogeneous class of conditions under the common rubric of recurrent depression (Goodwin & Jamison, 2007). Indeed, the example above of the individual with two episodes of depression, separated by over 50 years and signified by very different presentations, points to the limitation of episode number as the sole defining feature of recurrent depression.

The example above also points to the second feature of recurrent depression—episode timing—as a key defining consideration. Does it make good theoretical or clinical sense to designate a second episode of depression that occurs 50 years later as a recurrence? What about 20 years? Perhaps it makes better theoretical sense that two episodes separated by a relatively short period of time likely mark heightened vulnerability to repeated depressions. It also makes clinical sense in terms of treatment monitoring and prevention of future episodes. For example, the personal and societal tolls of depressions that occur at ages 22 and 77 are likely quite different than those of depressions that occur at ages 22 and 24; the latter has much more opportunity to progress to a highly recurrent condition, whereas the former is debatable in terms of the meaning of recurrent depression (e.g., as opposed to a new form of depression). Therefore, the most likely life course phenotype of recurrent depression is one with repeated incidences over relatively short intervals of time. This definition, taken as a starting point, could enhance ability to undertake research on predictors of individual differences in depression course.

Summary and Speculation

Our analysis to this point has targeted the basic conceptual and definitional system that has framed how recurrence is viewed and investigated. A major theme concerns the apparent paradox of depression, that the disorder can be both an acute, time-limited condition and a chronic and/or recurring one. A second emerging theme has been that depression may present a different clinical picture at different points in time over the life course (e.g., recurrence, relapse, chronic depression). Expanding on this latter topic...
may be of use for gaining a broader perspective on susceptibility to depression and on the lifetime course and overall morbidity associated with the disorder.

A life course perspective on relapse, recurrence, and chronic depression is illustrated in Figure 4. The first case is a true single lifetime episode case of depression (i.e., a SLED). The second example represents a classic case of recurrent depression, in which the index episode happens to be a FLED (but with the life course vantage point, not a SLED). The third example introduces the hypothetical alternative expressions of recurrent and chronic depressive episodes over the life course. Thus, although the index episode happens to be a chronic one, several other episodes over the life course are not and may more properly be regarded as additional recurrent episodes. Finally, the last case example extends the phenotypic possibilities over time to include relapse, recurrence, and chronic depression.

There could obviously be other life course profiles. For example, subthreshold depressive symptoms between episodes could represent another manifestation of depression liability worthy of taking into account, as such subclinical symptoms also have been found to predict relapse and recurrence (Judd et al., 1998). More generally, our purpose in Figure 4 is to illustrate how limiting a singular focus on the index episode might be and how a broader life course perspective could prove useful for research on major depression. Research on recurrence could examine whether or not chronic depression, relapse, recurrence, or subsyndromal symptoms represent alternative manifestations of a constellation of depressive presentations over the full life course. If some or all of these conditions cohere from this larger temporal vantage point, a strong case can be made for their inclusion as interchangeable indicators of recurrence or, more generally, as related indicators of an overarching time–severity–vulnerability construct of depressive morbidity. From a practical point of view, Figure 4 also suggests that through Balkanizing of relapse, recurrence, and chronic depression, the cumulative personal and societal toll of depression over the life course may have been markedly underestimated.

**Theoretical Implications: Design Deficiencies, Missing Persons, Prototype Studies**

Our goal in this next section is to trace the implications of the conceptual difficulties outlined above as they translate into problems for structuring and implementing research on recurrence. Although there is a large research literature on the general topic of recurrence in depression, the vast majority of the work is uninformative for the purposes of discovering which initially depressed...
individuals will and will not recur. This state of affairs becomes apparent when past research practices are evaluated in light of the conceptual confusion surrounding the basic acute versus recurrent nature of depression. As the following analysis reveals, a major problem is that past research practices have indiscriminately investigated the acute and recurrent forms of depression simultaneously and, thereby, each ineffectively.

**Conceptual Underpinnings of Current Design Deficiencies**

Figure 1 can be used to illustrate the problems associated with depression’s acute and chronically recurrent presentations. The downward slope of the recurrence trajectory is believed to be steep and swift, reaching an asymptote at roughly three lifetime episodes, as per the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM–IV–TR*; American Psychiatric Association, 2000; Mueller et al., 1999; Solomon et al., 2000). The preponderance of nonrecurrences permanently populates the far left side of this distribution, and relatively few nonrecurrences appear on the right side of the distribution. This suggests that not many people drop off the conveyor belt of depression after about three lifetime episodes. In contrast, recurrences are very common from relatively early on and become almost repeated certainties after only two lifetime episodes. This suggests that almost everyone moving toward the right end of the distribution is destined to recur time and again.

**Conflating acute and recurrent conditions.** One serious limitation of past research has been the indiscriminate manner in which predictors of recurrence have been investigated across the full range of recurrence histories. Past practices typically have enlisted participants in an index episode and then proceeded to evaluate risk indicators in relation to the number of lifetime episodes at that particular point in time (e.g., Hollon et al., 2006; Monroe, Slavich, Torres, & Gotlib, 2007). There are several reasons why this general approach may be insensitive for detecting predictors of recurrence.

This type of research design is biased toward recurrent conditions, owing to the disproportionate inclusion of many more cases with two or more lifetime episodes. That is, comparing currently depressed persons who can vary from one through eight or more lifetime episodes overrepresents recurrent cases (e.g., people with two or more episodes); cases that are acute and unlikely to recur are underrepresented. Consequently, the design is best suited for investigating predictors of recurrence for an already established recurrent group (e.g., people with two and more episodes). However, distinctions between, for example, individuals with five versus six lifetime episodes, or 14 versus 15 lifetime episodes, may not be especially informative. This is because all of these individuals are believed to have roughly an equivalent, extremely high risk for another recurrence (i.e., ~90%). Once a person has experienced two or more recurrences, there is relatively little variation in subsequent risk and little room for added statistical detection or clinically useful prediction.

Perhaps even more important is the theoretical possibility that the only difference between individuals with, for instance, a fifth versus a 10th episode is the arbitrary point in time at which the observations are made. This is based on the premise that a person with a fifth episode is most likely, given sufficient time, to become eventually a person with a 10th episode (i.e., a person with $n$ episodes is simply a future person with $n+1$, $n+2$, ..., $n+i$ episodes). As the number of recurrences rises, each instance of recurrence becomes less interesting from a theoretical perspective: It no longer represents what we want to predict. Rather, it has become what we have already predicted! What is theoretically interesting is investigating predictors of recurrence early on in the lifetime trajectory of depression, toward the far left side of Figure 1. This means more nuanced approaches are required to learn more about the acute nature of depression, which in turn will help to more precisely contour understanding of depression’s recurrent nature. In a sense, past studies of recurrence have been comparing apples with oranges, whereas in this particular instance one wishes to compare apples with oranges.

Overall, these observations strongly indicate that not all recurrences are of equal interest. Contemporary research investigating the full range of recurrences has been insensitive for detecting early risk indicators, inefficient in terms of investigator effort, and wasteful with respect to resources and statistical power. It is the distinctions between those who do and do not recur early in the life course of depression that should be prioritized.

**Future imperfect and a missing presence.** Another shortcoming of cross-sectional studies is that the number of lifetime episodes for any participant is only provisional and thereby is often an underestimate. Many participants will go on to experience many more recurrences. How this problem plays out over time is useful to examine.

As shown in Figure 1, a significant issue pertains to the very early lifetime course of depression. By definition, acute conditions can only be represented at the beginning of the distribution (i.e., one or perhaps two lifetime episodes in Figure 1). However, the recurrent conditions also must be represented initially at the beginning of the distribution but over time will progress to the right through the distribution. The early index episode lifetime cases (i.e., one or two episodes) consequently are the most heterogeneous with regard to a mixture of acute and (future) recurrent cases. As a consequence, the cross-sectional design yields an imbalanced picture of provisional lifetime recurrences, with cases currently having one or two lifetime episodes most likely to be in eventual error.

This imbalance is critical for evaluating research on predictors of recurrence. Comparison of first-onset cases with recurrent cases is problematic owing to the large proportion of those in the first-onset group who simply happen at that time to be experiencing their first lifetime episode but who eventually will become recurrent. Thus, the design is severely compromised for distinguishing acute from recurrent conditions. Yet, this confounding has been rarely if ever acknowledged as part of an explanation for the difficulties in detecting early indicators of risk for recurrence.

A final shortcoming of this genre of research is startling. Cross-sectional studies of recurrence are limited to information on people with differing histories of depression (i.e., have experienced one or more depressive episodes). This means that there is no direct information available on people who do not suffer another episode of depression (i.e., nonrecurrences). As a consequence, people who recur and people who do not recur cannot be contrasted in any straightforward manner with respect to risk indicators. As mentioned, though, information about people who do not recur is at the
heart of the research endeavor, so much so that it seems their presence has been taken for granted and their absence has gone unnoticed. Logically speaking, then, all that can be inferred from these cross-sectional studies is how people with differing histories of depression at one point in time may differ from one another with respect to risk indicators or correlates. Nothing can be inferred directly about how people who recur differ from those who do not.\(^5\)

Overall, cross-sectional studies on depression are poorly suited for investigating recurrence. To better understand recurrence and its potential predictors, we need direct comparisons between those who do and do not recur and not indirect comparisons between people who currently possess different episode histories, most of whom with time will continue to have more recurrences.

**Toward Resolving Depression’s Paradox: Targeting First Lifetime Episodes**

To our knowledge, no study has targeted a sufficient number of people in a first lifetime episode of depression, followed these incident cases over an adequate period of time, and made comparisons on a range of risk indicators between those who recur and those who do not recur. Some excellent studies, however, have approximated an ideal prototype for research that holds promise for discovering early indicators of recurrence risk. These studies provide useful guidelines on how such research may be undertaken and provide additional insights into why research on the acute nature of depression has been so uncommon.

**Retrospective research.** Although we have highlighted the limitations of common approaches to research on recurrence, there are productive ways in which retrospective procedures can be employed. For instance, a retrospective study could use detailed historical assessment to determine individuals’ lifetime histories of depression in the context of an epidemiological design. In theory, such research could detect those individuals who had experienced a first lifetime episode of depression and then determine who had suffered subsequent recurrent episodes and who did not. This type of research does require, however, reliable means of retrospectively acquiring essential information on the first onset of depression and the subsequent clinical status of study participants over a protracted period of time.

A noteworthy example is a study by Bland, Newman, and Orn (1986). These researchers retrospectively ascertained 75 patients over a 15-year period with a first lifetime hospital admission for unipolar depression. Graced with a record system providing reasonably detailed information and clinical follow-up, they determined that 42 individuals never again suffered a recurrence and, thus, could be reasonably assumed to be individuals with a SLED. The remaining 33 individuals recurred. These investigators then examined morbidity risk in 763 first-degree relatives and found that both family history and proband age of depression onset predicted who did and did not recur. The lowest morbidity risk for relatives was associated with those with a SLED having a late age of onset (3.4%), and the greatest morbidity risk was associated with recurrent cases having an early age of onset (17.4%).

Although there are inevitable challenges inherent in retrospective research in general (e.g., sufficient records and reliable information on clinical status) and in this study in particular (e.g., ascertainment with first lifetime admission vs. first lifetime episode), the Bland et al. (1986) report is unique in that it targeted people with a FLED and investigated two risk indicators, successfully finding factors associated with who does and who does not recur. In other words, it directly included people with a SLED as a comparison group. Therefore, we suggest that retrospective research that follows this design and focuses on assessment of depressive episodes has potential to uncover meaningful predictors of depression recurrence.

**Longitudinal research.** Prospective longitudinal research designs represent the gold standard for investigating the natural course of psychopathology. As noted previously, one of the premier sources of information on the longitudinal course of depression and its recurrences is the Collaborative Depression Study (CDS). Simpson, Nee, and Endicott (1997) provided the first article from this venerable project “to focus on the outcome of subjects with a first episode of MDD at intake” (p. 634). They reported on a sample of 197 depressed men and women and examined differences in the clinical course and recurrence of depression over a 15-year follow-up period. Unfortunately, however, Simpson et al. focused almost exclusively on sex differences in relation to recurrence. Although they acknowledged that other factors have been found to predict recurrence, there was no direct reporting of any other factors (e.g., age, history of prior episodes, family history of depression, other comorbid conditions). Rather, these other factors were statistically controlled to conservatively examine the role of sex in relation to timing of recurrence. (Overall, sex was found to be unrelated to recurrence, as is often the case; Burcusa & Iacono, 2007.) To our knowledge, this initial report on first-onset cases from the CDS is also the last report on this topic (despite some 38% of the depressed sample being in a first lifetime episode; Solomon et al., Table 1, p. 230). The potential importance of comparisons between first-onset participants who do and do not recur on a variety of risk indicators simply seems to have been overlooked.

More recently, a report drawn from the Baltimore site of the Epidemiologic Catchment Area Study culled out 92 cases with a first lifetime onset of MDD (Eaton et al., 2008). This investigation provides a very important counterpart to many other studies. By utilizing a population-based sample, Eaton et al. were able to overcome sampling biases associated with patient studies (e.g., the Berkson bias, the “clinician’s illusion”: Berkson, 1946; Cohen & Cohen, 1984). Significantly, Eaton et al. reported that approximately 50% of these first-onset cases recovered and did not experience another episode (even up to a maximum follow-up period of 23 years); about 15% had an unremitting course, and the remaining 35% recovered but experienced one or more recurrences.

Turning specifically to what might predict recurrences, however, the situation becomes more obscure. Eaton et al. (2008) noted

\(^5\) Admittedly, persons who currently have fewer lifetime episodes are far more likely to have future nonrecurrences in their midst than are depressed persons who already have experienced several lifetime episodes. As such, the implicit presence of nonrecurrences across different depression histories can conceivably yield crude clues about recurrence risk at an early stage in the life course of depression. The problems as we see it are that this approach (a) obscures the importance of information specifically on nonrecurrences; (b) supplants research that directly compares people who recur with people who do not; and (c) does not adequately take into consideration the concern that not all recurrences are of equal theoretical interest.
the difficulty in finding “any variables at all which predict recurrence” (p. 518), reporting that only an earlier age of onset forecasted a greater risk for recurrence. However, recurrence prediction was not the main goal in this important study, and thus a wide range of risk indicators was not investigated. Further, aside from the general statistics for an earlier age of onset predicting a greater likelihood of recurrence, the primary data on recurrence prediction were not provided (see Eaton et al., 2008, Table 2, p. 517). Instead, the study focused on (a) estimating the general long-term course of first-onset conditions, (b) distinguishing first-onset cases from nondepressed individuals, and (c) predicting the episode duration of first-onset cases.

An additional prototype of longitudinal research that addresses recurrence of depression is the Lundby Study (Mattisson, Bogren, Horstmann, Munk-Jørgenson, & Nettelbladt, 2007). This cohort study on a geographically defined population began in 1947 with 3,563 participants. In a recent publication, these investigators described the course and outcome for 344 subjects who developed their first onset of depression during the follow-up (between 1947 and 1997). These first-onset cases of depression were diagnostically heterogeneous (e.g., approximately 60% were MDD, with the remainder being different subtypes of depression, such as depression not otherwise specified or adjustment disorder with depressed mood). Mattisson et al. (2007) reported, “The probability of remaining free of recurrence was about 60% in the whole sample” (p. 8). Although this estimate was dependent on age at onset and length of follow-up period, these researchers emphasized the lower rate of recurrence relative to in- and outpatient samples. Once again, given the different objectives of the work, no information was provided on risk indicators for recurrence among these people with a FLED. Nonetheless, this study along with the Eaton et al. (2008) report provided consistent evidence for a lower rate of recurrence in community samples compared to patient samples, with 50–60% of incident depressed cases never suffering a recurrence. Thus, the prevalence of an acute and time-limited form of depression appears to be equal to or, possibly, exceeds that of the recurrent form of depression.

Summary. Existing retrospective and prospective studies on depression and recurrence have addressed a number of important topics and have provided valuable information regarding rates and timing of recurrence. However, the extant literature has invariably missed the mark for crisply comparing people with a FLED on a range of risk indicators with regard to who eventually does and does not subsequently recur over a reasonably protracted period of time. As a consequence, cases of depression that never recur remain a mystery. The basic challenge consequently is identifying nonrecurrences, in particular people who do not recur following a first lifetime episode, as they represent the critical comparison group.

On Defining, Documenting, and Investigating Acute and Recurrent Depression

A major challenge for research is that nonrecurrences can only be inferred indirectly: They are evidence in absentia. As long as observations are being made, recurrences provide definitive and concrete information, and nonrecurrences provide only probabilistic conjecture. In general, the longer the longitudinal investigation, the more secure the findings will be for differentiating those who recur from those with a SLED. But what happens when observations end? A nonrecurrence then becomes the absence of a past recurrence plus the projected absence of a future recurrence (in a sense, evidence in double absentia). But certainly, as we have shown, some people with a FLED will have a later recurrence, so a nonrecurrence, too, is to some extent also evidence in eventual error. Does this two-tiered, evidence in absentia, error-prone approach to defining and operationalizing people with a SLED pose serious threats to the validity of an acute form of depression or to the viability of research on the topic?

The challenges posed for defining and identifying those with a SLED present two concerns that require firm resolution. First, the provisional nature of any SLED designation raises the worry that eventually, over time, few if any of those with a SLED will remain (i.e., almost all will recur). This outcome would compromise the viability of research on people with a SLED (i.e., sufficient numbers for study) and, more important, would undermine the validity of our theorizing (i.e., if people with a SLED are so few in number, could they be theoretically informative for an acute form of depression?). Given the prevailing view in the literature that depression is a “highly recurrent illness” (Solomon et al., 2000, p. 229) a “highly recurrent disorder” (Burcusa & Iacono, 2007, p. 959) and that “single episodes are extremely rare if the period of observation is significantly extended” (Angst et al., 1973, p. 490), strong evidence for a significant presence of people with a SLED and the validity of an acute depressive subtype is needed.

Second, these definitional and operational challenges raise the specter that the only valid design for appropriately studying recurrence is one that follows people with a FLED throughout their entire lifetime. Such a life course design obviously poses major practical limitations and precludes a timely solution to the pressing problem of depression recurrence. Fortunately, there are practicable solutions for these concerns. We deal with these matters next.

Prevalence of SLED and Validity of Acute Depression

Information on lifetime rates of depression comes primarily from retrospective surveys (e.g., the National Comorbidity Survey Replication; Kessler et al., 2005). A major concern about retrospective surveys, though, is the consistent finding that many people with documented histories of depression when later interviewed fail to report past episodes. Not surprisingly, then, estimates based on retrospective methods are lower than estimates based on prospective methods, perhaps by as much as 50% (Andrews, Anstey, Brodaty, Issakidis, & Luscombe, 1999; Kendler, Neale, Kessler, Heath, & Eaves, 1993; Moffitt et al., 2010; Patten, 2009). On the surface, these data could cast doubts upon whether people with a SLED are prevalent and potentially available for research and whether acute depression exists in any meaningful form. For instance, many people with a SLED may report only one depressive episode, simply failing to recall or report other episodes.

Evidence addressing this matter recently was provided by Moffitt et al. (2010), who reported on lifetime prevalence of mental disorders (including depression) for the Dunedin, New Zealand, birth cohort study (N = 1,037), followed now through age 32 with a 90% retention rate. Lifetime prevalence rates from this longitudinal cohort design were approximately double the rates for retrospective surveys. For example, Moffitt et al. found the cumula-
tive lifetime prevalence for major depression up to age 32 to be 41.4%. Examining these data more closely, these investigators noted that 60% of those who were lifetime positive for depression had been diagnosed with the disorder at only one of the preceding longitudinal assessments. Further, Moffitt et al. (2010) hypothesized that “retrospective surveys may undercount primarily individuals who have relatively short-term disorder or single episodes” (p. 906).

These results do suggest caution when strictly retrospective methods are used to ascertain instances of SLED and the need for additional resources to include adjunctive, in-depth assessments to enhance sensitivity and detection of such cases in large-scale epidemiologic studies. But overall, the findings from this unique longitudinal cohort sample strongly imply that any measurement error in estimating lifetime risk for depression in past research most likely (a) works in favor of increasing the proportion of those with a SLED available in the depressed population at large (e.g., perhaps up to 60%) and (b) works against the concern that those with a SLED underreport other episodes of depression (and thereby are in fact recurrent cases).6

Reevaluating lifetime recurrence rates. More generally, the data in support of depression as an acute psychological condition, one that often does not become recurrent or chronic, are mounting. Some of the most thorough and representative research suggests that 50% to perhaps 60% of the initially depressed never recur (Eaton et al., 2008; Mattisson et al., 2007; Moffitt et al., 2010). These estimates for nonrecurrence stand in contrast to the official 40% estimate provided by the DSM. A closer examination of the bases for these prominent DSM estimates is revealing and suggests that updating may be in order (e.g., for DSM–5).

In the current DSM, it is stated that “at least 60% of individuals with Major Depressive Disorder, Single Episode, can be expected to have a second episode” (American Psychiatric Association, 2000, p. 372). Technically, though, this assertion does not appear to be accurate. According to the CDS reports from which these recurrence estimates are derived (see Solomon et al., 2000), there initially were 431 individuals with an episode of MDD. Of these, 65 were later reclassified and removed due to a subsequent change of primary diagnosis (to bipolar or schizoaffective disorder). This resulted in a final pool of 366 cases of pure MDD, of whom 318 eventually met criteria for recovery over a 10-year follow-up and were formally at risk for recurrence. Of these recovered cases (i.e., not all initial cases of MDD), 63.5% (n = 202) suffered a recurrence.

As we noted previously, what counts as a recurrence can be tabulated in several ways, and these different tabulations provide divergent impressions about the acute versus the recurrent nature of depression. If one takes the DSM phrasing literally (see above), all people with an initial episode of depression should be considered in the denominator. According to this interpretation, 202 of the 431 (46.9%) of the initially depressed individuals recurred. If one omits the initially depressed who subsequently had episodes of other disorders, 202 of 366 (55.2%) individuals recurred. It is only when the initially depressed who recover and who do not convert are included in the denominator that the data approximate the more commonly cited percentage of at least 60% (i.e., 202 recurrences for the 318 recovered cases; 63.5%). Although we acknowledge that there are definable reasons for the procedures adopted by Solomon et al. (2000), the fact remains that the recurrence estimates do not coincide with the explicitly stated objectives.

Even more critically, these CDS estimates commit the error of confusing an index episode of depression with a first lifetime episode of depression. Single lifetime cases represented only 38% of the CDS sample at the beginning of the study (and 25% of the initial sample already had experienced three or more lifetime episodes; Solomon et al., 2000). But there is no stratification of recurrence risk by prior episodes provided. What is investigated is the first prospectively observed recurrence following the intake index episode in a sample of predominantly highly recurrent individuals. In other words, this study did not provide recurrence risk estimates for genuine first lifetime cases (i.e., Major Depressive Disorder, Single Episode). Therefore, recurrence risk estimates for first-onset cases provided by DSM–IV are almost certainly inflated.7

There is yet another reason to suggest caution regarding the validity of the recurrence estimates based on the CDS. The CDS was a clinical sample, predominantly composed of inpatient cases (i.e., 74%; Solomon et al., 2000); such cases are likely to be more severe, as is indicated by the fact that 89% met the criteria for a definite or probable endogenous subtype (Solomon et al., 2000). This sampling bias could also inflate recurrence estimates (see also Eaton et al., 2008; the “clinician’s illusion”; Cohen & Cohen, 1984). It is hard to escape the conclusion that a 60% risk of recurrence for a first lifetime episode of major depression represents a significant overestimate and that figures approximating 40–50% may be more accurate (Moffitt et al., 2010).

Based upon these oft-cited DSM recurrence estimates appearing throughout the professional and lay literatures, it is evident that the manner in which these recurrence rates have been estimated and reported is not in keeping with the primary data or with the broader literature on recurrence. Yet, such statistical bits reinforce the impression of depression as a chronically recurrent disease, at the expense of recognizing that depression can also be an acute time-limited condition.

Longitudinal research on people with a SLED: A lifetime in waiting? It is clear from the above analysis that studies are needed that (a) recognize the importance of distinguishing those who do and do not recur early in the lifetime course of depression; (b) acknowledge that depression can manifest in both acute and recurrent forms (i.e., that one may be able to recover both from the episode and from the illness); and (c) include a sufficient follow-up time and a broad range of variables to establish valid

6 It could be contended that at least some of these younger people with a SLED will recur, suggesting that the current 60% reporting one lifetime episode will diminish over time. But it can also be contended that this would be compensated for by new incident cases of depression, which may be even more likely to be people with a SLED (i.e., less likely to recur owing to later age of onset and less time over which recurrences may come about). Also, even if it were the case that some people with a SLED look reporting of another episode, it would seem that they were not leading lives that were chronically impaired by depression. The larger point, that there are many people with a SLED in the population and available for research, appears secure.

7 It should be pointed out, too, this also implies that recurrence risk for those with several prior episodes is likely underestimated (due to the lower likelihood of first onset cases eventually recuring).
recurrence risk estimates and recurrence predictors. But are 32- to
year longitudinal cohort studies the only means to procure valid
data? Probably not. Although time may at first appear to work
against the investigator, it is not really an enemy; over due course,
time becomes, if not a friend, a good working companion for
research on recurrence.

First, as noted earlier, a probable clinical course characteristic of
recurrent depression is one with repeated incidences over rela-
tively short intervals of time. This implies that investigators should
be able to procure sufficient numbers of recurrences over reason-
ably short intervals of time (e.g., 2 or 3 years) and that those with
a FLED will be pruned relatively quickly to yield increasingly
stable estimates of final SLED status. Second, from a theoretical
point of view, rapid recurrences following onset of FLED may be
especially important for detecting early risk indicators of a recur-
lent lifelong course. As noted above, the more quickly recurrences
come about, the more likely the life course trajectory will devolve
into repeated recurrences and related morbidities. Indeed, as
discussed previously, new episodes occurring remote in time from the
initial episode may not even be true recurrences.

Third, a key problem is that past research has predominantly
studied people with several recurrences, the majority of whom will
recur again (see Figure 1). When the happy fact is recognized that
perhaps only 50% of first-onset cases (i.e., those with a FLED) will
ever recur (Eaton et al., 2008), other common research practices
come into question and previous risk estimates require additional
correction. A recent multicenter prospective study by Kanai et al.
(2003) illustrates this point nicely. These investigators followed an
inception cohort of previously untreated patients with unipolar
major depression (N = 95), citing a median time to recurrence of
over 6 years. Kanai et al. (2003) remarked that this was “much
longer than previously reported in studies employing similar def-
nitions but dealing with a more severe spectrum of patients” (p.
839). From a practical standpoint, this lengthy span of time ap-
pears ominous for implementing research on recurrence.

One problem with the statistical design of the Kanai et al. (2003)
study and, hence, with the derived median time to recurrence
statistic is that it relied on Kaplan–Meier analyses to depict sur-
vival curves. Survival analyses, however, are predicated upon the
assumption that all participants, given adequate time, eventually
will experience the event under study, in this case a recurrence.
However, as we now recognize, not all individuals with depression
will suffer a recurrence, even if followed for a lifetime. Indeed, the
majority of patients in the Kanai et al. study were individuals with
a FLED (n = 67), of whom only 50–60% would be expected to recur
at all. Therefore, for those with a FLED the median time to
recurrence would be the time required for approximately 25% of
the full sample (i.e., 50% of the sample expected to ever recur) to
become depressed again. As such, the Kanai et al. median time to
recurrence statistic is very likely an overestimate. Using their data
and current estimates, we can recalculate a more accurate time to
recurrence estimate for the Kanai et al. sample that indicates a
longitudinal follow-up period of approximately two years is suf-
ficient to capture the majority of recurrences following an initial
onset.

We can estimate, based on previous research, the likelihood of
recurrence for the people with a FLED (n = 67) and recurrent (n =
28) cases separately and then project the combined recurrence rate
for the entire sample. For those with a FLED, an estimated 50%
recurrence rate is in keeping with recent longitudinal epidemi-
ologic data (e.g., Eaton et al., 2008). In the Kanai et al. (2003) data,
then, this suggests that 33.5 of the 67 people with a FLED will
never recur (i.e., are people with a SLED). For the recurrent subset
of the sample, recurrence estimates are complicated by the lack of
specific information about the number of prior episodes. Accord-
ing to the DSM estimates, recurrence rates in cases with more than
three lifetime episodes are 90% (American Psychiatric Associa-
tion, 2000). Therefore, if we assume that the mean number of
lifetime episodes in the Kanai et al. recurrent group was at least
three, then about 25 can be expected to recur and about three will
not. For the sample as a whole, this provides a cumulative yield of
58.5 individuals who recur at least once (33.5 from those with a
FLED, 25 from those with recurrence) and 36.5 individuals who
never have another depressive episode (33.5 from those with a
FLED, three from those with a prior recurrence). Overall, we can
project based on these calculations that approximately 62% of the
Kanai et al. sample should experience at least one recurrence of
depression over the entire life course and that about 38% should
not.

How do the empirical data of Kanai et al. (2003) compare with
our projections based on the accumulated evidence base? Of the
original 95 patients in their study, 50 recovered from their index
episode and completed the follow-up protocol (32 who recovered
were lost to follow-up). By 72 months postrecovery, 31 patients
had experienced at least one recurrence and 19 patients had never
experienced a recurrence. Thus, 62% of the remaining sample (31
of 50) had recurred and 38% (19 of 50) had not. These numbers
precisely match our projected absolute rate of expected recur-
cences over the entire life course (62%). That is, all of the patients
in the Kanai et al. sample who would ever be expected to recur did
so within the 72 months of the study.

Therefore, the “median time to recurrence” more properly char-
acterizes the time required for all recurrences to take place. Prac-
tically speaking, this means that within 6 years researchers can
garners the vast majority of projected lifetime recurrences (not
simply half of the anticipated lifetime recurrences). Moreover,
with an awareness that the return of depression following recovery
diminishes at a negatively accelerating rate over time, the median
time to recurrence for people with a FLED will be considerably
less. Indeed, based on the Kanai et al. figures, a plausible estimate
for the median time to recurrence is closer to 12 months (see Kanai
et al., 2003, Figure 2, p. 843).9

Summary. Many sources of information indicate that acute
and time-limited forms of depression are very common among
people who have become depressed and perhaps approach 60% of
the population of depressed people (Moffitt et al., 2010). Official
estimates of depression’s lifetime course should incorporate the
fact that, for some people, depression is not a lifelong disease.
Finally, additional data and ideas strongly support the viability of

8 Note, also, that if relapse and recurrence represent an artificial distinc-
tion, the time frame required is considerably less than we presently esti-
mate.

9 Kanai et al. (2003) counted the beginning of the required 8-week
recovery period as the starting point for estimating the well period. We
therefore subtracted 2 months in deriving our estimate from the figure
provided, for a .75 cumulative survival rate.
investigating people with a FLED, a recurrence, or a SLED over relatively circumscribed periods of time. Research on recurrence and its predictors can be undertaken with greater potential power and sensitivity, and such research can be accomplished without requiring lifetime longitudinal protocols.

Further Considerations and Recommendations for Future Research

Discovering early risk indicators for which initially depressed persons will and will not recur now appears more promising and achievable. Most generally, researchers need to target first-episode depressed persons, evaluate a range of risk indicators that may distinguish those that do and do not eventually recur, and do so over a follow-up period capturing the time period of greatest recurrence risk (e.g., 2 years). Some further considerations may be of value as a guide for future inquiry.

Optimizing SLED–Recurrence Comparisons: Dynamically Updated Designs

An important benefit of longitudinal designs that follow first lifetime episode cases is that these designs can be dynamically updated by changes in participant status over time. This not only means a sorting and shifting of people with a FLED into either a provisional SLED or recurrence, but also a fine-tuning of initial FLED into other more valid diagnoses based on long-term course (e.g., removing people who develop mania or schizoaffective disorder). This iterative process provides a strong method for converging on increasingly valid characterizations of a SLED and recurrence over time.

Dynamically updated designs, too, can provide a means of enlarging perspectives on the lifetime clinical course of depression and its associated morbidities. Figure 3 again illustrates this broader perspective. Prior research has tended to tidily divide cases of depression over relatively short spans of time into those who remit, relapse, recover, recur, or remain chronic. However, these time-limited and specific foci may blind investigators to conceptualizing larger frameworks that better capture the full range of morbidities associated with depression over time. It might be expected that those with the greatest liability not only experience repeated recurrences but on other occasions experience relapses, chronic depressions, or intermorbid subsyndromal symptoms. We will be able to evaluate such possibilities and begin to envision others only when the scope of the inquiry is expanded to allow for such alternative conceptualizations and research.

Optimizing SLED–Recurrence Comparisons: Who and When?

With the specific objective of discovering early harbingers of recurrence risk for those with a FLED, how might general comparisons between those who do and do not recur most usefully proceed? The most straightforward approach is to directly compare people with a FLED who experience a first lifetime recurrence and who do not (people with a SLED). However, as hinted at in Figure 1, this might not provide the optimal comparison. The vast majority of people who do not suffer recurrences have either one or two lifetime episodes (approximately 40–60% and 30% respectively; American Psychiatric Association, 2000; Eaton et al., 2008; Moffitt et al., 2010). In contrast, only 10% of people with three lifetime episodes are projected to not recur again, a threefold drop-off from a second lifetime episode (and fourfold from a FLED). This suggests that the first lifetime recurrence group remains heterogeneous with respect to future likelihood of recurrence (18 of 60 will not recur) and consequently may not be the optimal group for sensitive comparisons with people with a SLED.

It may be the second recurrence group—those cases that have a total of three lifetime episodes—where the lifetime course of recurrent depression begins to crystallize (i.e., only four of 42 people do not recur). Consequently, the optimal design may prove to be one in which risk indicators are compared for groups based on individuals with a provisional SLED versus individuals having experienced three lifetime episodes.

A second task for future research can be envisioned in relation to Figure 1 as well. This would be to locate cases with one lifetime recurrence in relation to those with a SLED and in relation to the multiple recurrent groupings (e.g., three or more lifetime episodes). The group of twice-ever depressed individuals may prove to be especially informative for understanding the liability differences between those with a SLED and those with a recurrence. For example, we anticipate that the twice-ever depressed group will be similar in susceptibility to individuals with a SLED rather than the multiple episode grouping. This is based on the premise that the twice-ever depressed and those with a SLED are people who remain vulnerable to depression yet may require exposure to unusual and impactful circumstances to trigger another episode. We wish to point more generally to the fertile research possibilities that emerge when people with a SLED are explicitly represented and considered in the research agenda on recurrence.

Some Remaining Practical Challenges

Research on recurrence taking advantage of the unique characteristics of first lifetime cases (those with a FLED), as well as incorporating a life course perspective, holds considerable promise for advancing understanding of depression and its recurrences. We have argued that undertaking such research is quite feasible. However, we envision that such work will not always be easy to implement. In particular, two remaining practical challenges for future research might benefit from some discussion.

First, many, if not most, people with a FLED may not identify themselves initially as depressed. Further, these people may rarely seek treatment at such an early stage of their illness. Additionally, people with a FLED who eventually become people with a SLED may be especially difficult to identify and recruit. Therefore, is it possible to identify those with a FLED and those with a SLED without doing lengthy epidemiological assessments?

There are now a small number of studies targeting people with a SLED that have used creative strategies to developing these cohorts. Community recruitment strategies that focus on the period of greatest risk for first lifetime onset (e.g., screenings in high schools and colleges; Alloy et al., 2000; Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2000) or that collaborate with primary care have the potential to identify those with a FLED. Multisite collaborative investigations would further enhance sample size and increase generalizability. We fully acknowledge that longitudinal research targeting people with a FLED and people with a SLED...
will require more resources in terms of time and recruitment; however, these risks are outweighed by the benefits of this research for providing a fuller and more valid understanding of depression recurrence risks and rates.

The second challenge concerns the practical utility of the life course perspective we propose. The basic problem is simply that of time in evaluating whether chronic depression, relapses, and recurrence stem from a common underlying liability that takes on different expressions over time. For example, a substantial proportion of those with a FLED will not remit within 2 years and are commonly designated as chronic depression (Hollon et al., 2006; Klein, 2010). Following these chronically depressed persons until at least some of them remit and then tracking them with respect to relapse and recurrence will take years (and many resources). More generally, the span of time required for one person to have multiple expressions of possible depressive equivalents will require a long-term longitudinal commitment. And without adequate resources to ensure prolonged coverage, results from such studies can be misleading. For example, the longer it takes for a participant to recover, the less time may be available for subsequently detecting a recurrence (Belsher & Costello, 1988).

In order to better investigate these premises, prospective research on individuals experiencing a FLED can be complemented with retrospective approaches involving persons with recurrent depression, persons who relapse, or persons with chronic depression. With appropriate methodologies to expand the observation period (e.g., Keller et al., 1987), the picture of alternative depressive phenomena over time can be portrayed and the premise of a common underlying vulnerability can be more formally evaluated.

**Liability to Depression Over Time: Considering Recurrences and SLEDs**

The final consideration involves the scope of predictors to include for distinguishing acute from recurrent depression. Although first-incidence cases of depression were all susceptible to depression initially, this group is heterogeneous in terms of susceptibility to recurrence (i.e., about half will recur, half will not). How and when such liability differences arise remains unclear but is of central theoretical importance for guiding where and when to look for differences in risk indicators.

The simplest case is for the individuals with a FLED who recur. These individuals may differ from those with a SLED in terms of their initial liability to future depressions, even prior to their first onset. Alternatively, they may acquire increased liability in some manner following onset of the first episode (e.g., kindling or scarring phenomena; Burcusa & Iacono, 2007; Monroe & Harkness, 2005). Future research that is capable of addressing both initial between group differences on risk indices, as well as within-group changes on risk indices, will prove to be of most value in providing the needed observations.

The situation is less straightforward with regard to acute cases that do not recur (i.e., those with a SLED). Here, in contrast to the recurrence situation, the theoretician needs to explain how someone of proven vulnerability escapes depression’s return in perpetuity. This topic has rarely been considered. Assuming stable liability implies that, although remaining vulnerable, people with a SLED somehow elude any additional episodes of depression.

We speculate that at least one pathway involves good fortune. Whatever the circumstances that were sufficient to initiate the first lifetime episode, they coalesce only once over the person’s life. Perhaps relatively severe forms of acute stress are required, perhaps during periods of other heightened susceptibility (e.g., lowered social support), which renders it unlikely that the coincident conditions coalesce very often to transform the predisposition into the pathology (Meehl, 1977). Many people may possess the diathesis for depression and go about their lives in varying degrees from its edge, but fortunately do not fall over—at least not very often (Andrews, Poulton, & Skoog, 2005; Monroe & Simons, 1991).

Indeed, some of the best available evidence is consistent with the premise of stable vulnerability but relatively low to moderate risk. As noted, approximately 40% to 60% of individuals with a FLED do not recur (American Psychiatric Association, 2000; Eaton et al., 2008; Moffitt et al., 2010), yet perhaps 30% of individuals with a second lifetime episode do not recur. In contrast, only about 10% of people with three lifetime episodes do not recur—a threefold drop-off from a second lifetime episode. This is in keeping with the idea that liability remains stable and relatively low for some initially depressed persons and that relatively extreme initiating circumstances are required to trigger episodes of depression in those who are less strongly predisposed (see, e.g., Eaton et al., 2008).

Alternatively, liability may change for the acute, single lifetime cases of depression. But because the person never incurs another depressive episode, it seems quite improbable that liability increases. Is it possible, though, that liability decreases? Could some people who become depressed once become less prone to become depressed again? This suggests not only that these people become personally less vulnerable to depression but that they potentially become even less vulnerable than people who have never before been depressed. Whether or not people with a SLED become less vulnerable is an admittedly tricky matter, given available information and biases in present research. The existing data probably are weaker and more indirect for such a position than they may seem at first glance. For example, because the only currently available indicator of vulnerability change is dependent upon whether or not someone eventually recurs, it is difficult if not impossible to determine whether people with a SLED remain stably vulnerable or become less so. This is because, by definition, those with a SLED cannot recur, and if recurrence is our only presently available indicator of vulnerability, our hands are tied for adjudicating between these theoretical possibilities (i.e., stable vs. decreasing liability). Nonetheless, we think speculations about liability changes over time in relation to people with a SLED are important for two reasons: (a) It seems very plausible to assume liability does not increase for those with a SLED (which is counter to most current thinking about depression); (b) attempting to explain why previously depressed people escape a recurrence forces a broader conceptual approach to considering both risk and resilience (e.g., Belsky & Puess, 2009).
Lavori, Keller, & Klerman, 1984; Nesse, 2000; Southwick, Vythilingam, & Charney, 2005).

Concluding Summary and Remarks

It is clear that for many people, depression commonly results in recurrent episodes over the life course. It should now be equally clear that for many people, depression commonly is an acute, time-limited condition. Current estimates suggest that these two outcomes constitute roughly an equal proportion of the currently defined depressed population. As yet there is little information available to guide researchers and clinicians in understanding which of these two life course pathways any particular person with a first-incident case of depression eventually will follow. We hope it is now clear that a pressing goal is to discover these early indicators of recurrence risk.

The concept of recurrence is the natural focal point that separates acute from recurrent cases of depression. We have seen how contemporary conceptual systems that frame and define recurrence provided a useful beginning for research on the clinical course of depression. Whereas at the time they were introduced these ideas brought needed attention to the recurrent course of depression, they may now prejudice ideas and research in ways that distort the overall picture of depression over time and impede progress in the quest to find early predictors of recurrence risk. How to better conceptualize and characterize major transitions in affective functioning over the clinical course of a depressive episode and a person’s life represent fertile topics for future research.

The task is twofold. First, within the time frame of a single episode, the validity of alternative recurrence definitions should be addressed empirically. Determining which are the most useful parameters for operationalizing recovery and, thereby, recurrence represents an essential next step for investigators. In particular, distinctions between recurrence and relapse are more or less meaningful depending upon how one sets these operational criteria for defining recovery. Whether or not two separate constructs are even necessary deserves further examination. Present conventions are not based upon quality data but rather upon “the literature, clinical experience, and logic” (Rush et al., 2006, p. 1842). These matters have wide-ranging implications and are far too important to be inferred from an unquestionably underdeveloped research literature.

The second task pertains to the lifetime course of depression. This extends the question of discriminant validity between recurrence and relapse to the discriminant validity between recurrence and other possible expressions of the liability to depression over the life course. On the one hand, this suggests a possible collection of alternative phenotypes over time for the recurrent group (e.g., including relapse and some forms of chronic depression). For example, the particular presentation of an episode may be influenced by a different set of factors that influence the course of an episode of depression once begun (Brown & Harris, 2008). On the other hand, a life course perspective can also accommodate the suspected heterogeneity of depression and etiologically distinct forms of the disorder. This allows for a reconsideration of the assumption that depressed persons can recover “from the episode, but not from the illness” and encourages evaluation of the idea that not all additional lifetime episodes of depression are necessarily recurrences. A life course perspective could add richness to the descriptive psychopathology of natural course of depression over time and provide a better accounting of its associated overall morbidities.11

Equally apparent, though, is the fact that depression very often does not take a severe lifelong course. This alternative provides a critical counterpoint to the prevailing ideas about depression as a recurrent, lifelong disease. But because these single lifetime cases have fallen between the cracks of theory, research, and practice, it is not surprising that almost nothing is known about them. This class of formerly depressed persons requires detailed attention and analysis. For example, do such persons recover completely and lead “normal” lives? Do they experience chronic or recurring subsyndromal symptoms that impair functioning and impede full participation in and enjoyment of life? Do they develop other comorbid psychiatric conditions? How can it be that someone of proven vulnerability to depression escapes any further episodes? Much is to be learned about these people, and we hope that much will be gleaned about the nature of depression from such efforts. It is unfortunate that the clinical literature is silent about these individuals, for they represent a ray of hope for those suffering from depression.

It is these single lifetime cases of depression, too, that represent a beacon of hope for theory and research on depression and its lifetime course. Without the active presence of nonrecurrent cases in conceptual models or research protocols, theoreticians and researchers cannot progress in meaningful ways. Awareness of this situation casts the pessimistic picture of early risk indicators of recurrence in a new light. For example, there is essentially no research comparing single lifetime and recurrent cases on a range of pre-, peri-, or postmorbid clinical characteristics, let alone on relevant biological, psychological, and social factors. Although the field is ripe for such multilevel forms of inquiry, we acknowledge that the task is a complicated and challenging one. We hope that by addressing the pitfalls of the best investigative practices to date, we have helped forge the foundations for productive research on recurrence of depression.

Finally, our theoretical attention has been confined to foundational conceptual matters involving the construct of recurrence, along with the clinical course of depression over time. More specific conceptual models of recurrence address particular etiological processes to explain individual differences in susceptibility to recurrence. For example, there may be subtypes of depression that are genetically prone to suffer repeated recurrences (Burcusa & Iacono, 2007; Kendler et al., 2001; Maher, Hughes, Zubenko, & Zubenko, 2010) or liability to depression that may accrue over time with successive stressors and depressive episodes (e.g., the kindling hypothesis; Monroe & Harkness, 2005; Post, 1992). Another agenda for the field is to reinvigorate these specific conceptual models for recurrence with discussion and debate fueled by the ideas we have raised in the present article. It is our hope that such work will overturn the tide of pessimism regarding predicting recurrence and rejuvenate research that eventually leads to advances in treatment and prevention.

11 Considering subsyndromal conditions further increases the likelihood of underestimating depression’s personal and societal consequences (Judd et al., 1998).
References
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Correction to Monroe and Harkness (2011)

In the article “Recurrence in Major Depression: A Conceptual Analysis,” by Scott M. Monroe and Kate L. Harkness (Psychological Review, Advance online publication. September 5, 2011. doi: 10.1037/a0025190), an incorrect version of Figure 2 was published, and Figure 3 was published in color instead of Figure 4. Also, in Table 1, the acronym “(FLED)” should not have been included in the Recurrence section, under Confusion to avoid, following “Not to be confused with a first lifetime recurrence.” All versions of this article have been corrected.

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