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A lifetime approach to major depressive disorder: The contributions of psychological interventions in preventing relapse and recurrence

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HIGHLIGHTS

- CBT delivered during the acute phase, does appear to have an enduring effect.
- Continuation psychological treatment appears to reduce risk for relapse.
- Preventive interventions have the largest effects for ultra high-risk individuals.

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ABSTRACT

Major depressive disorder (MDD) is highly disabling and typically runs a recurrent course. Knowledge about prevention of relapse and recurrence is crucial to the long-term welfare of people who suffer from this disorder. This article provides an overview of the current evidence for the prevention of relapse and recurrence using psychological interventions. We first describe a conceptual framework to preventive interventions based on: acute treatment; continuation treatment, or; prevention strategies for patients in remission. In brief, cognitive-behavioral interventions, delivered during the acute phase, appear to have an enduring effect that protects patients against relapse and perhaps others from recurrence following treatment termination. Similarly, continuation treatment with either cognitive therapy or perhaps interpersonal psychotherapy appears to reduce risk for relapse and maintenance treatment appears to reduce risk for recurrence. Preventive relapse strategies like preventive cognitive therapy or mindfulness based cognitive therapy (MBCT) applied to patients in remission protects against subsequent relapse and perhaps recurrence. There is some preliminary evidence of specific mediation via changing the content or the process of cognition. Continuation CT and preventive interventions started after remission (CBT, MBCT) seem to have the largest differential effects for individuals that need them the most. Those who have the greatest risk for relapse and recurrence including patients with unstable remission, more previous episodes, potentially childhood trauma, early age of onset. These prescriptive indications, if confirmed in future research, may point the way to personalizing prevention strategies. Doing so, may maximize the efficiency with which they are applied and have the potential to target the mechanisms that appear to underlie these effects. This may help make this prevention strategies more efficacious.

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Major depressive disorder (MDD) has a highly recurrent nature (Kessler et al., 2005; Kupfer, Frank, & Phillips, 2012), which is why one of the most important challenges in the management of MDD is the prevention of depressive relapse and recurrence. Individuals who suffer from a first depressive episode have a 40% to 60% chance experiencing a subsequent episode; individuals with 2 episodes have an approximate 60% chance; and individuals with three episodes the risk is as high as 90% (Eaton et al., 2008; Moffitt et al., 2010; Solomon et al., 2000). Such statistics emphasize the importance of interventions that can disrupt patterns of repeated depressive relapse/recurrence and enable sustained remission and recovery. Cosci and Fava (2013) recently hypothesized an integrated model of staging for unipolar depression in line with concepts used in the medical field and developmental psychology. For this staging model 5 stages were defined, which will require empirical validation. Stage 1 represents the prodromal phase including mood symptoms (sad mood, subsyndromal depression) and symptoms with mild functional decline (generalized anxiety, irratibility, anhedonia, sleep disorders), stage 2 represents the acute depressive episode, stage 3 the residual phase characterized by mood symptoms (depressed mood, guilt, hopelessness), dysthymia, and symptoms comparable to the prodromal phase (except anhedonia) and additionally anorexia and impaired libido. Stage 4 is characterized by recurrent depression and double depression and the last stage refers to chronic depression (as defined by DSM, lasting for a least 2 years (American Psychiatric Association, 2000)). Interventions that aim to prevent relapse/recurrence can either be applied in stage 2 (acute phase, examining prophylactic effects of acute psychological interventions) and in stage 3, the residual phase.

To guide this discussion, we first provide the operational key definitions of key change points in depression including response, remission, recovery, relapse and recurrence. Subsequently, we consider leading theories that explain the heightened vulnerability for MDD, followed by an overview of the types of psychological preventive strategies and its empirical evidence for the enduring effects of the psychological interventions. We next describe empirical evidence which subtypes of patients have the best outcomes in the acute phase, continuation phase, and preventives therapies available, (i.e., what preventive strategy works best for whom). We then review putative mediators; that is mechanisms underlying the effectiveness of psychosocial interventions with the potential to reduce relapse and recurrence. Finally, future directions for research are explored and recommendations for clinical practice are provided.

1. Definitions of response, remission, recovery, relapse and recurrence

Consensually agreed definitions for the constructs of response, remission, recovery, relapse and recurrence facilitate to comparisons across studies. The 'MacArthur Research Network on the Psychobiology of Depression' proposed operational criteria for each term (Frank et al., 1991) to guide the field. Fig. 1 depicts the main change points in the course of depression (Kupfer, 1991). For clarification we use this heuristic and propose the following definitions of episode, response, remission, partial remission, recovery, relapse, and recurrence in Table 1, modified somewhat from Frank et al. (1991); we also added the definitions of stable and unstable remission as they are implicated in the findings we discuss below.

We begin by noting that all references to response, remission, recovery, relapse and recurrence, start with reference to an existing or prior episode of depression. In the current diagnostic framework (American Psychiatric Association, 2013), an episode of MDD is defined as the presence of at least 5 of 9 possible symptoms for a period of at least two weeks, and with one of two key criterion symptoms being present (sad or depressed affect, and loss of interest or pleasure in usual activities, more days than not in the 2 week period). In most research, the episode that is used as the point of reference for the other events

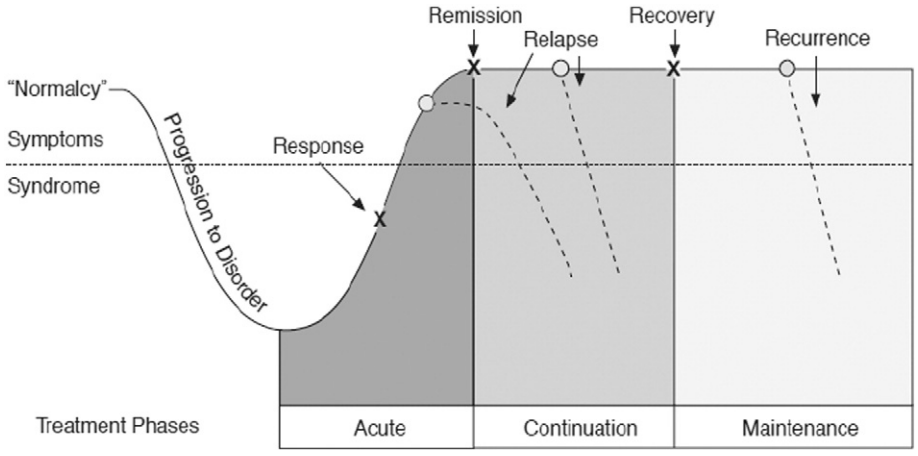

Fig. 1. Definition of response, remission, recovery, relapse, and recurrence (Kupfer, 1991). Note that acute phase treatment aims to promote a response as well as some level of remission. Continuation phase treatment aims to sustain remission, prevent relapse, and promote recovery. Maintenance phase treatment aims to foster or sustain recovery and prevent recurrence.

Table 1
Definitions of change points in depression (adapted from Frank et al., 1991).

Term	Definition
Index Episode	Major Depressive Episode (MDE), as defined by a diagnostic system such as the DSM-V (American Psychiatric Association, 2013), lasting at least 2 weeks, and from which decisions about response, remission, recovery, relapse and recurrence are made.
Response	A reduction in symptom severity relative to baseline status (usually 50%) that is often taken to imply that acute-phase treatment is having an effect.
Remission	A period of time (often defined as two months or longer) when symptoms have largely normalized and the patient can be thought of as well. (Note that remission precedes both recovery and recurrence).
Stable remission	A sustained interval in which depressive symptoms are absent or quite minimal.
Unstable/partial remission	An interval during which some level of depressive symptoms are present (partial) or only sporadic (unstable).
Recovery	The end of the index episode following an extended period of remission (e.g., 6–12 months). The notion here is that the patient is no longer in episode.
Relapse	The reemergence of symptoms of depression (presumably part of the index episode) following some level of remission but preceding recovery.
Recurrence	The onset of a new episode of depression following an extended period of remission of sufficient duration to assume that recovery had occurred.

(e.g. remission, recovery, etcetera) is termed the *index* episode (also referred to as stage 2; the acute stage), to distinguish it from other possible past and future episodes.

The term *response* as a construct is usually used to refer to improvement over the course of treatment and is often assumed to indicate that treatment may be working (although that improvement could be occurring for unrelated reasons). Response is sometimes operationalized in terms of no longer meeting diagnostic criteria for an episode of major depression (which is an absolute index that denotes change only in the sense that the patient previously met diagnostic criteria) or not exceeding a maximum score on a symptom severity rating scale like the Hamilton Rating Scale for Depression (HRSD, Hamilton, 1960). However, most often (at least in the pharmacotherapy literature) it is defined as a proportionate reduction from baseline on an established rating scale or self-report for assessing severity of depressive symptoms (e.g. HRSD, IDS-R, BDI). Response may be partial, if residual symptoms of the index episode remain, or may be complete, in that the patient returns to a pre-episodic level of functioning (or perhaps even better). We propose a reduction in symptom severity relative to baseline status (usually 50%) that is often taken to imply that acute-phase treatment is having an effect.

The term *remission* as a construct implies that the patient has essentially normalized (is no longer symptomatic) and is often operationalized in terms of a maximal level of symptoms over a given period of time. For example, the MacArthur group defines remission operationally as a period of at least two months during which the patient experienced only minimal symptoms (HRSD scores of 7 or less) (Frank et al., 1991). Whereas response implies that the patient is better, remission implies that they are well. Some investigators go further and differentiate between stable remission, in which symptom levels never rise above the defining threshold, and either partial or unstable remission, in which there are occasional flurries of symptom elevations such that the patient either remains mildly symptomatic or experiences oscillations between being asymptomatic and mildly symptomatic (Jarrett & Thase, 2010; Jarrett et al., 2001; Segal, Williams, & Teasdale, 2013; Segal et al., 2010). Generally, the more stable the remission the better the long-term prognosis. Both the response and remission phase could be a part of stage 3 of the staging model, including the residual phase as characterized by mood symptoms and non-depressive symptoms.

The term **recovery** as a construct is used to denote the end of the index episode following an extended period of remission, often operationalized in terms of 6–12 months without relapse. The notion here is that the patient is no longer thought to be in episode. Depression is thought to be a self-limiting but episodic disorder in which each episode is likely to resolve on its own in the absence of treatment (spontaneous remission) although subsequent episodes are likely to recur. It is generally assumed that antidepressant medications suppress symptoms without necessarily altering the course of the underlying episode and that patients need to be kept on mediations long enough for the index episode to resolve before being taken off treatment. In essence, a remitted patient may look well symptomatically but is not truly over the underlying episode until enough time has passed that he or she can be considered to have recovered.

The terms relapse and recurrence both refer to a clinically significant deterioration following a period of symptomatic improvement. Although there is some inconsistency across the literature, the term **relapse** as a construct is usually used to designate the reemergence of symptoms of depression (presumably part of the index episode) following remission but preceding recovery, with the implication that the underlying episode has not yet run its course and is being kept at bay only by the ongoing treatment. By convention, treatment extended past the point of symptomatic improvement (including remission) is referred to as **continuation treatment** and its aim is to prevent relapse. The term **recurrence** as a construct is used to denote the onset of a wholly new episode of depression following an extended period of remission of sufficient duration to assume that recovery has occurred (stage 4 according to the staging model). Again by convention, treatment extended past the point of recovery for the purpose of preventing recurrence is referred to as **maintenance treatment**. Relapse typically is operationalized as the reemergence of the index episode within approximately 6–12 months after initial remission (but before recovery), whereas recurrence typically is operationalized in terms of the emergence of symptoms sufficient to warrant being considered an episode again after that point (see Table 1, Frank et al., 1991). Although different investigators tend to differ somewhat in the specific ways in which they operationalize these constructs, the one thing about which there is general agreement is that response precedes (and is less complete than) remission and that remission must precede recovery (which requires a longer duration of symptomatic improvement). Any return of symptoms between remission and recovery is considered to be a relapse (the return of the treated episode) and any return of symptoms following recovery is considered to be a recurrence (the onset of a wholly new episode).

That being said, we note that there is so much variability in how different investigators operationalize these various constructs (and in some instances even reverse the definitions) that we have chosen to collapse the two into a single index of relapse/recurrence and will use the two terms interchangeably throughout the rest of the chapter, except when the study design or finding allows us to differentiate these outcomes. Different investigators all agree that both refer to a reemergence of symptoms following a period of relative wellness but there is not sufficient consistency in the definitions of the constructs or the ways in which they each have been operationalized to be able to tell whether an study is focused on relapse or recurrence.

2. Vulnerability hypotheses for relapse/recurrence in MDD

Several explanations have been given for the high relapse/recurrence risk in MDD, but most are based on either the idea of a) individual differences in premorbid vulnerability, or b) "scarring" as a result of one or more depressive episodes. Burcusa and Iacono (2007)described the premorbid vulnerability hypothesis such that "individuals at high risk for multiple episodes already possessed the necessary characteristics to make them prone to recurrent depression, and that these necessary characteristics existed even before their first episode" (p. 980). In essence, some individuals are just at greater risk than others (due to a yet to be identified factor) and that risk does not change across the course of successive episodes. In contrast to the premorbid vulnerability hypothesis, the scarring hypothesis purports that each subsequent

episode leaves residual effects that increase vulnerability for the next episode. That is, the very process of going through an episode of depression produces a change in underlying causal factors that increase the risk of having future episodes. Possible causal mechanisms underlying the scarring hypothesis have been described for biological factors, such as genetics (Lok et al., 2013), the HPA axis (Lok et al., 2012), cognitive factors (implicit and explicit cognitive factors, Elgersma, Glashouwer, Bockting, Penninx, & de Jong, 2013) and stress-related factors (Beshai, Dobson, Bockting, & Quigley, 2011; Kok et al., 2013; Lok et al., 2013; Teasdale et al., 2000). This area is ripe for more rigorous tests. Longitudinal cohort designs and primary prevention studies including higher-risk groups selected before their first episodes may prove useful (e.g. Lewinsohn, Rohde, & Seeley, 1995; Ormel et al., 2012; Penninx et al., 2008). Such studies must measure the putative risk mechanisms (be they biological and/or psychological) across time to determine the extent to which: 1) the mechanisms change with subsequent episodes, 2) are modifiable through psychological treatments, and 3) explain treatment outcomes. Secondary prevention studies within randomized controlled trials, including tests of mediation, continue to be needed to establish if such treatments work through their hypothesized mechanism (e.g. Batink, Peeters, Geschwind, van Os, & Wichers, 2013; Bockting, Elgersma, et al., 2011; Bockting, Kok, et al., 2011; Kuyken et al., 2010; Williams et al., 2014).

3. Relapse/recurrence prevention strategies

Most people in the Western world who seek help for their depression receive antidepressant medication (ADM) (Olfson & Marcus, 2009). Not surprisingly, the modal strategy to prevent relapse after remission is continuation ADM (Geddes et al., 2003; Glue, Donovan, Kolluri, & Emir, 2010; Hansen et al., 2008; Kaymaz, van Os, Loonen, & Nolen, 2008). However, there is also evidence that indicates that the effects of antidepressants are smaller than presumed (Gøtzsche, 2014) and have harmful effects for elderly (Coupland et al., 2011).

There is no evidence that ADMs reduce subsequent risk when discontinued; and indeed symptoms frequently re-emerge when ADMs are discontinued (Geddes et al., 2003; Glue et al., 2010; Guidi, Fava, Fava, & Papakostas, 2011; Hansen et al., 2008; Imel, Malterer, McKay, & Wampold, 2008; Kaymaz et al., 2008; Oestergaard & Møldrup, 2011; Pigott, Leventhal, Alter, & Boren, 2010; Vittengl, Clark, Dunn, & Jarrett, 2007). Adverse effects of use of antidepressants have been reported as well, especially based on observational (clinical) studies (Fava, 2014; Gøtzsche, 2014). Meta-analyses indicate that continuation ADM reduces the risk of relapses/recurrence compared to pill-placebo, although the odds ratios are modest, ranging from 0.12 to 0.35 (Geddes et al., 2003; Glue et al., 2010; Hansen et al., 2008; Kaymaz et al., 2008). However, it is not clear how long ADMs need to be continued. Leading international guidelines typically recommend that patients be kept on medication following remission, but disagree somewhat with respect to how long that should be. The American Psychiatric Association recommends keeping patients with a history of recurrence on continuation ADM for at least from 4–5 months (American Psychiatric Association, 2010), whereas NICE (2010) recommends a period lasting from 1–2 years to prevent both relapse (continuation treatment) and recurrence (maintenance treatment). In point of fact, however, studies on the preventive effect of continuation and maintenance phase ADMs often had a follow-up period no longer than single year, suggesting that such guidance is based on clinical consensus rather than evidence from randomised controlled trials with follow-ups that lasted more than two years.

Psychological interventions have been developed that have at least three potential types of preventive effects: 1) acute phase psychological treatments as typically applied in stage 2 (during the depressive episode) with prophylactic effects that endure after the actual interventions are discontinued; 2) ongoing preventive effects of continuation psychological interventions for patients who have responded or remitted to an acute phase treatment; and, 3) indicated psychological relapse prevention strategies that start after remission for patients (stage 3; the residual stage) who either have previously responded to treatment (e.g. acute phase ADM some other type of acute phase psychological treatment) or who are presently in remission (including patients that did not receive treatment) but are at risk for future episodes.

4. Prophylactic or enduring effects following discontinuation of acute phase treatment of MDD

In contrast to acute phase ADM treatment, some types of acute phase psychological interventions appear to have preventive effects for some period of time even after discontinuation (Cuijpers et al., 2013; Vittengl et al., 2007). Cognitive behavioral therapy (CBT) has been studied the most often. The Vittengl et al. (2007) meta-analysis included 28 studies, (N = 1,880 adults), of which 16 examined the prophylactic effect of acute CBT. After discontinuation of acute-phase treatment, relapse/recurrence rates were lower in those patients previously treated with CBT than in those patients previously treated with ADM (39% vs 61% over 68 weeks). This meta-analysis further suggested that acute phase CBT also reduced relapse/recurrence when it was combined with acute phase ADM (22% reduction if combined versus 23% reduction if not combined), but this comparison was based on only three studies available involving 615 patients (Evans, Hollon, DeRubeis, & Piasecki, 1992; Hautzinger, de Jong-Meyer, Treiber, & Rudolf, 1996; Simons, Murphy, Levine, & Wetzel, 1986). Therefore, the absence of differences (essentially a null finding) should be considered with caution, as the authors note. A subsequent meta-analysis also compared the long-term effects of CBT versus ADM and included three additional studies (n = 9 studies; 6 overlap with the meta-analysis Vittengl meta-analysis; N = 506 patients). These results confirmed the finding that acute CBT has an enduring effect following treatment termination not found for ADM (Cuijpers et al., 2013). In other words, individuals who responded to acute phase CBT were less likely to relapse/recur following treatment termination than those who responded to acute phase ADM (OR = 2.61, 95% CI 1.58–4.31, $p < 0.001$). Moreover, patients who responded to acute phase CBT were no more likely to relapse/recur following treatment termination than patients kept on continuation ADM. The fact that relapse/recurrence proportions varied significantly among the studies reviewed in the meta-analyses may reflect differences in: inclusion/exclusion study characteristics, follow up period, acute phase treatment characteristics, outcome (e.g. time to relapse versus relapse rates), relapse definitions and types of assessment (Cuijpers et al., 2013; Vittengl et al., 2007). However, what was relatively constant across the trials was the magnitude of the difference favouring prior CBT over prior ADM.

5. Enduring effects of other psychotherapeutic approaches following acute phase discontinuation

The Vittengl et al. (2007) meta-analysis also compared the prophylactic effect of acute CBT to other acute psychotherapeutic approaches. Only four such studies were available including, behavioural interventions, interpersonal psychotherapy (IPT) and psychodynamic-interpersonal therapy. The meta-analysis produced comparable relapse rates for acute CBT relative to other psychological interventions (25% for acute phase CT versus 29% over other depression-specific psychological interventions, over a mean period of 92 weeks). This might suggest that other types of psychotherapies share CT's enduring effect. However, as the authors caution, this overall null finding may reflect the small number of studies. Moreover, none of those four studies found an advantage for any of the interventions (including CT) relative to any other condition; that is, all reported null findings in designs in which CT did not outperform control or prior medication conditions. Additionally, two of the four included studies focused on behavioral interventions that are typically part of a CBT intervention (Gortner, Gollan,

Dobson, & Jacobson, 1998; Jacobson, Fruzzetti, Dobson, Whisman, & Hops, 1993). In fact, yet another study published after that meta-analysis found prior CT superior to prior ADM and comparable to continuation medication, with prior BA not differing from prior CT (or ADM withdrawal). These data are suggestive that a more purely behavioral intervention might also have an enduring effect. The remaining two studies compared prior CBT to other psychotherapeutic approaches including interpersonal psychotherapy (IPT) (Shea et al., 1992) and psychodynamic-interpersonal therapy (Shapiro, Rees, Barkham, & Hardy, 1995). The only indication that the interpersonal approaches in those studies might have had an enduring effect was that they did not differ from CBT, but CBT as implemented did not separate from prior ADM in one study (Shea et al., 1992) and no such comparison was included in the other (Shapiro et al., 1995). At this time, there is little evidence that either acute phase IPT or psychodynamic-interpersonal therapy have enduring effects other than the fact that they did not differ from acute phase CBT in studies in which that latter intervention showed little evidence of an enduring effect as implemented.

In summary, acute phase CBT (and possibly behavioral activation) appears to reduce the risk of subsequent relapse beyond the end of treatment (for meta-analyses see Cuijpers et al., 2013; Vittengl et al., 2007; for reviews see Beshai et al., 2011; Hollon et al., 2005; Kuyken, Dalgleish, & Holden, 2007). Acute phase CBT also might reduce the risk of recurrence, as it did relative to medication withdrawal in the two studies in which patients treated with prior acute phase CT were compared to patients who were withdrawn following a year of continuation ADM (Dobson et al., 2008; Hollon et al., 2005). No studies have examined whether other psychotherapies have enduring effects that extend to the prevention of recurrence.

5.1. Continuation phase cognitive therapy

While acute phase CT may prevent more relapse compared to acute phase ADM when both are discontinued, the rate overall rate of relapse is often high and clinically unacceptable. For example, studies suggest that the effect of acute phase CBT on prospective relapse report high rates as demonstrated in meta-analyses (29% within 1 year, and 54% within 2 years) (Vittengl et al., 2007). A second relapse prevention strategy is to continue the same modality to which the patient responded in the acute phase. Jarrett and colleagues developed and tested a continuation phase CT (C-CT, Jarrett et al., 1998, 2001; Jarrett, Vittengl, & Clark, 2008) to prevent relapse and promote full remission in adult outpatients who responded to acute phase CT. Responders to acute phase CT who received 8 months of continuation phase CT were significantly less likely to relapse (10%) compared to those who received the assessment only control (31% relapse). Over the full 24-month follow-up, both age of onset and quality of acute phase remission moderated preventive effects. In adults who became depressed at 18 years or earlier (early onset), C-CT reduced relapse and recurrence strikingly relative to the assessment only control (16% vs 67% respectively). Similarly, in responders with unstable remissions, C-CT reduced relapse and recurrence to 37% compared to the 62% in the assessment only control.

Continuation phase CT can be prescribed strategically for the individuals who need it most, including those at higher risk for relapse and recurrence. This strategy was demonstrated in a sequential 3 stage RCT (Jarrett & Thase, 2010) that focused on adults with recurrent MDD who responded or partially responded (i.e., no MDD; HRSD-17 less or equal to 12) to acute phase CT. Responders with, unstable remission, defined as one or more a Hamilton Rating Scale for Depression [HRSD] scores of 7 or more during the seven final assessments during acute phase CT), were randomized (N = 241) to matched pill placebo (PBO) or fluoxetine (FLX) or C-CT. Both active continuation phase treatments (either fluoxetine or C-CT) reduced relapse significantly more than pill placebo over the 8 months that the treatment was provided in responders to acute phase CT at higher risk for relapse (relapse rates: 18.3% for C-CT; 18.0% for FLX; and 32.7% for PBO). After discontinuation of continuation phase treatment, acute phase CT responders were followed for another 24 months. Overall, no differences in recurrence rates emerged over the full 32 months, suggesting that the relapse preventive effects of C-CT do not differ from the standard of care (continued FLX) and that either reduces relapse more than PBO in CT responders who are at higher risk for relapse. Since all patients responded to acute phase CT. It is worth noting that the overall rate of relapse/recurrence over 32 months was lower than would be expected for patients with recurrent MDD at higher risk (relapse rates: 45.2% for C-CT, 41.1% for FLX and 56.3% for PBO). It is possible that the prophylactic effects of acute phase CT endured after discontinuation and obscured differences in the interventions for these high-risk responders.

6. Preventive effects of other psychotherapeutic continuation/maintenance approaches

Several studies have examined the preventive effects of other psychotherapeutic treatments compared to ADMs. Frank, Kupfer, Perel, and Cornes (1990) compared the effect of monthly continuation IPT versus ADM (imipramine) + clinical management versus IPT + ADM versus IPT + PBO versus PBO + clinical management, in a randomized controlled trial including 128 participants with recurrent depression. They reported the longest survival time for the group that combined monthly continuation of IPT + ADM (131 weeks). The patients that received either ADM or IPT in the continuation phase had a significantly longer time to relapse/recurrence of depression compared to the groups that did not receive either continuation treatment. Direct comparisons between the IPT and ADM groups were not possible because of a limited of statistical power.

In another study, women who had been treated to remission (defined as 3 consecutive weeks of HRSD scores of equal to or less than 7) with acute IPT or with combined IPT and ADM (N = 132) were assigned to weekly, biweekly, or monthly continuation IPT. No significant differences in relapse rates were found across weekly, biweekly of monthly continuation of IPT (Frank et al., 2007). In addition, they reported a significant difference in time to relapse/recurrence in women that received only IPT (84 weeks) versus women that received IPT and ADMs (54 weeks). The majority of women that received acute IPT (and recovered) stayed well (74%) if IPT was continued after remission over 2 years. The relapse/recurrence rate for women that received an acute combination treatment was about double of those who only received acute IPT followed by continuation of IPT. However, since women were randomized after the end of acute phase treatment, no firm conclusions can be drawn about the most effective sequence of treatment. Studies with sufficient statistical power are needed to examine the preventive effect of continuation phase IPT and to examine whether monthly IPT sessions are sufficient to protect against relapse and recurrence.

Reynolds et al. (1999) used a randomized controlled trial, to compare continuation phase ADM and IPT versus PBO and IPT versus PBO alone versus ADM in 107 recovered (HRSD <10) elderly depressed participants. They reported that recurrence was significantly reduced in all three active treatment groups compared to pill-placebo condition over a three-year period. Relapse/recurrence rates were the lowest for the combination of ADM and IPT (20%), with ADM alone next (43%), then IPT alone (64%), and highest in pill-placebo (90%). Post-hoc analyses indicated that patients who were 70 and older benefitted less than those aged 60 to 69 (Reynolds et al., 1999).

Reynolds et al. (2006) compared the preventive effects of maintenance ADMs (paroxetine) and monthly IPT in the elderly. They randomized 116 participants that (partially) remitted with the combination of ADMs (paroxetine) and IPT. Patients were assigned either to maintenance ADM (paroxetine) plus monthly clinical management sessions, monthly IPT plus PBO, ADM plus monthly IPT, and, PBO plus monthly clinical management sessions. The authors reported the following

relapse rates respectively; 37%, 58%, 35%, and 68%, indicating that monthly IPT did not reduce relapse rates, while ADMs did.

In summary, continuation phase CBT appears to reduce risk of relapse (for meta-analyses see Cuijpers et al., 2013; Vittengl et al., 2007) and there are indications that continuation and maintenance phase IPT might also reduce risk for relapse and recurrence, although evidence in that regard is more mixed. More research is needed to determine whether other depression-specific continuation phase therapies might have preventive effects.

7. Indicated psychological relapse prevention strategies after remission

Another strategy to prevent MDD is to start a preventive psychological intervention for patients who are at high risk for relapse/recurrence by virtue of some negative prognostic factor but who are currently in full or partial remission (indicated psychological relapse prevention strategies as applied in stage 3; the residual stage). These are preventive strategies that are specifically developed to prevent relapse and recurrence (i.e. Wellbeing Cognitive Therapy, Fava, Rafanelli, Grandi, Conti, & Belluardo, 1998; Fava et al., 2004; MBCT, Teasdale et al., 2000; Preventive Cognitive Therapy, Bockting et al., 2005). Most studies included a mixed group of patients who were either treated in the acute phase with ADMs or psychotherapy (alone or in combination), treatment-as-usual, or who had no treatment but were in remission at the time of enrollment to the study. Most studies evaluated relatively brief interventions, such as 8 sessions of MBCT or PCT (Bockting, 2010).

Indicated psychological strategies such as MBCT, Wellbeing CT and Preventive CT seek to prevent relapse/recurrence in patients at risk can be effective in preventing relapse and recurrence over follow-ups of at least a year (Guidi et al., 2011; Piet & Hougaard, 2011; Vittengl et al., 2007). A meta-analysis of Piet and Hougaard (2011) focused exclusively on studies of MBCT + usual care vs usual care alone and MBCT versus m-ADM (6 studies including 593 participants; 3 studies overlapped with the Guidi meta-analysis, and 2 with the Vittengl meta-analyses). MBCT + TAU significantly reduced the risk of relapse/recurrence with a risk ratio of 0.66 for MBCT compared to TAU or PBO controls, corresponding to a relative risk reduction of 34%. The relative risk reduction was 43% for participants with three or more previous episodes, while no risk reduction was found for participants with only two episodes.

Behavioral activation has yet to be applied in a sequential fashion (that is, starting behavioral activation after remission on other types of treatments), but is another promising candidate since it has been found to be effective in preventing relapse in the one study in which it has been tested (Dobson et al., 2008).

A meta-analysis of Guidi et al. (2011) examining the specific effect of indicated brief psychological relapse prevention strategies after remission compared to ADMs and/or TAU included eight studies(Bockting, Spinhoven, Koeter, Wouters, & Schene, 2006; Fava, Rafanelli, Grandi, Canestrari, & Morphy, 1998; Fava et al., 2004; Kuyken et al., 2008; Ma & Teasdale, 2004; Paykel et al., 2005; Perlis et al., 2002; Teasdale et al., 2000) with 442 patients receiving a brief psychological preventive intervention and 433 in a control treatment arm (ADMs or treatment as usual). The pooled risk ratio (RR) for relapse/recurrence was 0.80 [95% confidence interval (CI) 0.66–0.96], suggesting a relative advantage in preventing relapse/recurrence for the brief preventive CBT interventions compared with control conditions. A nonsignificant trend favoring psychological interventions during ADM continuation compared to ADM alone or treatment as usual (TAU) was reported (RR 0.84, 95% CI 0.67–1.05). Patients randomized to the psychological interventions while their ADMs were discontinued were significantly less likely to experience relapse/recurrence compared to controls (RR 0.65, 95% CI 0.46–0.91).

Given the scientific debate on the overestimated effects of antidepressants, adverse effects of use of antidepressants and the reported difficulty to stop antidepressants because of (long term) withdrawal symptoms (Fava, Bernardi, Tomba, & Rafanelli, 2007; Gøtzsche, 2014), alternative relapse prevention interventions are valuable. Starting preventive psychological interventions after remission on ADMs represents a promising alternative strategy to long-term use of ADMs, especially for individuals who are at the greatest risk of relapse, as two recent meta-analyses indicate (Guidi et al., 2011; Piet & Hougaard, 2011). However, few studies randomized remitted participants after tapering ADMs in combination with starting a psychological intervention versus continuation of ADMs. Recent small scale RCT studies suggest that MBCT may be an alternative to continuation ADM (Kuyken et al., 2008; Segal et al., 2010). Among patients in full or partial remission on m-ADM, Kuyken et al. (2008) asked if MBCT plus support to taper/discontinue antidepressants (n = 62) could be a viable alternative to staying on m-ADM (n = 61) over a 15-month follow-up. Relapse/recurrence rates over 15-month follow-ups in the MBCT group that tapered ADM were 47%, compared with 60% in the continuation/maintenance phase ADM group. Segal et al. (2010) randomized 84 patients with recurrent depression that remitted on ADM to either continuation of ADM, tapering ADM and MBCT versus tapering of ADM while switching to PBO. There was a significant interaction between the stability of remission at baseline and subsequent prevention of relapse (P = .03). Among unstable remitters (1 or more Hamilton Rating Scale for Depression score >7 during remission), patients in both MBCT and maintenance ADM showed a 73% decrease in hazard compared with PBO (P = .03), whereas for stable remitters (all Hamilton Rating Scale for Depression scores ≤7 during remission) there were no differences between MBCT versus ADM versus PBO in time to relapse/recurrence. Although these post hoc findings require replication in larger samples, especially for participants with higher levels of residual symptoms, active relapse prevention strategies appear promising. Further studies are needed to examine the specific and/or comparative effects of these relapse prevention strategies. A recent meta analyses including a large variety of studies on meditation programs, including MBCT, for psychological stress and well-being, found that no evidence of superiority of meditation programs compared to other active treatment (i.e. medication, behavioral therapy, exercise) on several outcomes, including positive mood (Goyal et al., 2014). Currently, larger scale trials are in progress to address the question whether a psychological intervention can be an alternative for continuation/maintenance ADMs (MOMENT study, Huijbers et al., 2012; PREVENT study, Kuyken et al., 2010; Break the rhythm of depression study, Bockting, Elgersma, et al., 2011; Bockting, Kok, et al., 2011).

Overall, studies show that providing preventive CBT after remission (Wellbeing CT, MBCT, Preventive CT) reduces the risk of relapse. Large-scale studies are needed to validate this positive long-term effect of psychological interventions as an alternative to continued use of ADMs. Behavioral activation has yet to be applied as relapse prevention strategy after remission, but is another promising candidate since it has been found to be effective in preventing relapse in the one study in which it has been tested (Dobson et al., 2008).

7.1. What works for whom and how?

One of the critical questions in the field of prevention science is to find out what preventive strategy works best for whom. Understanding the predictors of differential response to different treatments (moderators) can help us target these treatments to the patients most likely to benefit from them (precision medicine). Prognostic factors for poor prognosis in general or within one given treatment or class of treatments can be differentiated from prescriptive factors that indicate differential response to different kind or phases (acute versus continuation) of treatments (Fournier et al., 2009).

A greater number of previous episodes of depression and more residual depressive symptoms are robust predictors of increased rates of depressive relapse and recurrence (e.g. Burcusa & Iacono, 2007; Kessing, Hansen, Andersen, & Angst, 2004; Mueller et al., 1999). In four selected preventive studies the effect of preventive CT or MBCT depended on the number of previous episodes (Bockting, Spinhoven,

Wouters, Koeter, & Schene, 2009; Bockting et al., 2005; Ma & Teasdale, 2004; Stangier et al., 2013; Teasdale et al., 2000). Specifically, the preventive effect of either CT or MBCT (relative to controls) was larger the greater the number of previous episodes, while the risk of relapse/recurrence increased with episode number in the treatment-as-usual condition (Bockting et al., 2005; Bockting et al., 2009; Ma & Teasdale, 2004; Stangier et al., 2013; Teasdale et al., 2000). In the first three studies, the protective effect was absent in patients with only two previous episodes (note that no patients were included with a single index episode). This converges with a recent relapse prevention study of Stangier et al. (2013) that found that patients with three and four previous episodes benefited from a basic intervention including psychoeducation, while patients with more than four previous episodes seemed to require a specific, targeted relapse prevention treatment consisting of combination of preventive CBT and MBCT. This prescriptive indication, i.e. the apparent indication that number of episodes can be used to determine for whom preventive CBT or MBCT is likely to be beneficial, should be interpreted with caution because of the modest sample size. Notably, other relapse prevention studies did not find that the number of previous episodes was a prescriptive factor (Geschwind, Peeters, Huibers, van Os, & Wichers, 2012); in some studies the numbers of patients with < 3 prior episodes was very small (Jarrett, Minhajuddin, Gershenfeld, Friedman, & Thase, 2013; Jarrett et al., 2001; Ma & Teasdale, 2004; Teasdale et al., 2000), and other studies did not include a single episode group and a group with two previous episodes (Guidi et al., 2011). Whether the number of previous episodes is a prescriptive factor for preventive psychological interventions versus other interventions or controls requires exploration in further studies with long term follow ups.

Other potential prescriptive factors include the stability of remission (residual depressive symptoms) and age of onset, as indicated by a study of Jarrett et al. (2001, 2013) and Segal et al. (2010). Jarrett et al. (2013) showed that both age of onset and quality of acute phase remission moderated treatment effects for C-CT. In adults who became depressed at 18 years or earlier, C-CT reduced relapse and recurrence to 16% compared to the assessment only control (67%). Similarly in responders with unstable remission, C-CT reduced relapse and recurrence to 37% compared to the 62% in the assessment only control. Further, Jarrett et al. (2013) demonstrated that in higher risk responders (those with unstable remission: responders with a score of 7 or more on the HRSD during the seven final assessments during acute phase CT), the relapse preventive effects of C-CT do not differ from continuing ADMs and that either reduces relapse more than PBO over the 8 months that the active treatments are in effect.

Segal et al. (2010) also found that stability of remission might be a prescriptive factor for preventive treatment. That is, stable remitters (all Hamilton Rating Scale for Depression scores ≤7 during remission) profited less from active preventive treatment, while unstable remitters (1 or more Hamilton Rating Scale for Depression score >7 during remission) profited more from active treatment (either MBCT of ADM after remission). While it may be that patients who respond to treatment and have a stable remission simply do not require ongoing treatment and therefore appear to benefit less than patients with unstable symptoms(see also Jarrett et al., 2001), these findings will profit from replication in a larger sample.

Williams et al. (2014) randomized 274 remitted participants with a history of three or more episodes to MBCT versus Cognitive Psychological Education (CPE) versus Treatment as Usual (TAU). No differences in relapse were found between MBCT and the active control treatment (CPE) or TAU (i.e., risk of relapse over 12 months follow-up; hazard ratio for MBCT vs. CPE = 0.88, 95% CI [0.58, 1.35]; for MBCT vs. TAU = 0.69, 95% CI [0.42, 1.12]. Post hoc analyses, however, revealed that severity of childhood trauma increased relapse risk and significantly interacted with treatment. Patients with higher severity of childhood trauma benefited more from MBCT than either CPE or TAU (hazard ratio was 0.61, 95% CI [0.34, 1.09], for MBCT vs. CPE, and 0.43, 95% CI [0.22, 0.87], for MBCT vs. TAU). Hypothesis driven replication of these sub-group effects is needed, before firm conclusions can be drawn from this study.

We have promoted concepts that map onto important change points in the course of major depressive disorder (see Table 1). If used consistently across the field of mood disorders, these heuristics may aid researchers in discovering the variables associated with improvements in long-term outcomes, such as recovery, and differentiate these from shorter range outcomes such as response. We note that durations of treatment may to be associated with differential outcomes for distinct patient subtypes, which will aid in solving public health problems associated with making affordable care available for all people. Focus on longitudinal outcomes, paired with effective treatment strategies, will increase that likelihood that research findings impact patients' and families lives in meaningful ways.

In summary, continuation CT and preventive interventions started after remission (CBT, MBCT) seem to have the largest differential effects for individuals that need them the most, that is those who have the greatest risk for relapse and recurrence (i.e. those with unstable remission, more previous episodes, potentially childhood trauma, early age of onset). We suggest that future study designs should attend to these prescriptive risk factors and include longer-term follow-ups that can determine potentially important moderators of treatment outcome. These studies will answer important question about what works for whom.

8. Mediators of and mechanisms within preventive psychological interventions

To improve the efficacy of preventive psychological strategies it is important to identify and understand what mechanism(s) make(s) the treatment work. Theoretically, both acute-phase and preventive CT target cognitive vulnerability (e.g., underlying dysfunctional beliefs) as a key mechanism linked to relapse that the treatment seeks to change. These risk factors are presumed to be latent in the nondepressed or remitted phase, but are triggered by life events, stress or sad mood. According to the classical cognitive theory underlying CBT, change in the negative *content* of dysfunctional beliefs precedes symptoms reduction and a reduced risk of relapse (cf. Beck, Rush, Shaw, & Emery, 1979; Clark, Beck, & Alford, 1999). Thus, CBT appeared to modify, or at least compensate for a hypothesized underlying mechanism of relapse. Jarrett, Vittengl, Doyle, and Clark (2007)examined the durability of change in the *cognitive* content in recurrently depressed participants (N = 156), after their acute phase CBT. Improvement in cognitive content was durable over a 2-year follow-up. Continuation-phase CBT further improved cognitive content, but only on one measure. While the durability of cognitive change is evident, whether cognitive change is the active mechanism in preventive effects or the active mechanism in deterioration is in need of further study. Since dysfunctional beliefs were hypothesized to depend on dysphoria, both the 'differential activation' hypothesis of Teasdale (1988)and the 'mood state' hypothesis of Miranda and Persons (1988) have shifted the focus from studying unprimed dysfunctional beliefs towards primed beliefs by activation of these beliefs. These studies typically assess beliefs before and after a mood induction (e.g., elicited by a task such as sad music to lower mood) as a risk factor for relapse/recurrence of depression. Three studies have found support for the notion that cognitive reactivity predicts subsequent relapse following remission from MDD (Kuyken et al., 2010; Segal, Gemar, & Williams, 1999; Segal et al., 2006). However, two studies found no evidence for cognitive reactivity as risk factor for relapse in participants remitted from MDD (Jarrett et al., 2012; van Rijsbergen et al., 2013), although Jarrett and associates showed that unprimed dysfunctional attitudes did predict relapse and recurrence. Thus, evidence is mixed for the role of cognitive reactivity being a risk factor for relapse in MDD but substantial evidence links dysfunctional attitudes to depressive relapse and recurrence (Beshai et al., 2011; van Rijsbergen et al., 2013). It is possible that preventive CBT might protect against relapse and recurrence because it makes negative schema less accessible after

exposure to repeated depressive episodes (Hollon, Stewart, & Strunk, 2006). Further studies are needed to examine specifically the impact of psychological interventions on the accessibility of negative and positive schema in recurrent depression and its association with subsequent relapse and recurrence.

Mindfulness based CT emphasizes *process*, as well as the *content*, of thinking (Teasdale et al., 2000, 2001). Studies indeed indicate that cognitive reactivity after MBCT predicts relapse and recurrence (Kuyken et al., 2010; Segal et al., 1999, 2006) relative to ADM. In addition, Kuyken et al. (2010) found indications that MBCT works by cultivating mindfulness and compassion and that learning self-compassion appears to break the potential link between mood reactivity and depressive symptoms one year later. However, studies that examine "true" mediation by change in cognitive reactivity, before versus after (MB)CT, on the effect of preventive psychological interventions are as yet missing. Standard CBT might also change the *process* of thinking, rather than just the *content* of thinking, as demonstrated in several trials (Paykel et al., 1999; e.g. Teasdale et al., 2000, 2001). Indeed, preventive CBT might encourage participants to carefully focus on, or tolerate, or accept thought contents and feelings and processes, without trying to change them (to judge, avoid, or suppress thoughts).

Preventive psychological interventions may also work because they directly target prognostic factors such as residual symptoms and thereby reduce the risk of relapse (Fava, Fabbri, & Sonino, 2002; Geschwind et al., 2012; Jarrett et al., 2001; Thase, Simons, McGeary, & Cahalane, 1992). However, as few studies have directly tested mediation of preventive psychological interventions in relapse and recurrence prevention, further research is required to understand the working mechanism of current effective relapse and recurrence-prevention strategies, such as preventive C-CT (Jarrett et al., 1998); CBT and MBCT. As these processes are better understood, treatments can improve by targeting key mechanisms involved in depressive relapse/recurrence (Beshai et al., 2011; Bockting, Elgersma, et al., 2011; Bockting, Kok, et al., 2011).

9. Future directions

In summary, acute phase psychological interventions (especially CBT and possibly BA) have prophylactic effects that reduce the risk of relapse in depression after treatment termination. However, relapse rates can be further reduced by continuation CT and there are some indications that continuation IPT (if continued on a regular basis) also reduces risk of relapse. Few studies examined the effect on recurrence. Starting preventive CBT after remission (Wellbeing CT, MBCT, Preventive CT) also reduces risk of relapse.

Further research should examine prescriptive factors in preventing relapse and recurrence (i.e. which approach works for whom) and identify underlying causal mechanisms of acute, continuation, and starting preventive psychological treatment of depression after full or partial remission. Instability of remission as marked by the presence of residual depressive symptoms is a robust risk factor with prescriptive value. Perhaps the number of previous episodes, age of onset, childhood trauma may also prove to offer prescriptive benefit. Future studies should examine these factors in further detail and determine whether less intensive interventions such as psycho-education are especially beneficial for people with the relatively lower risk (Stangier et al., 2013), while targeted interventions like C-CT, preventive CBT, and MBCT are *effective* in people with the highest risks for relapse and recurrence. If this prescriptive finding holds with preventive psychological interventions, it will be particularly important since continuation phase ADM appears to be less effective in preventing relapse/ recurrence for the patients with the higher risks (Kaymaz et al., 2008). For example, a meta-analysis suggests that individuals with recurrent depression experience less protection from ADMs (OR = 0.37) compared to individuals that experienced a single episode (OR = 0.12). Adverse effects of use of antidepressants have been reported as well, especially based on observational (clinical) studies (for a review see Fava, 2014) and should be studied further in controlled trials. Potential detrimental effects of the combination of antidepressants with psychological interventions should be studied in randomized controlled trials (Bockting et al., 2008; Fava, 2014).

Long-term studies with ongoing evaluations over a 5–10 year period are needed to determine whether these preventive psychological interventions indeed have the most potential for people with depression that have the worst prognosis in term of relapse and recurrence, compared to other treatments, including ADMs. Longitudinal follow-ups that are long enough to assess recurrence are important and not well studied at this time.

In addition, we have to be aware that a patient might be treated with several types of treatments over time, while current randomized controlled trials usually study 1–2 treatments within a patient, regardless of the clinical history and co-morbidity. Smaller studies might be needed first, to examine the effects of (sequential) treatments in specific groups, for instance in groups with co-morbid symptomatology (Fava, Tomba, & Tossani, 2013).

Current clinical practice guidelines for MDD treatment recommend long-term monitoring and guidance for individuals with recurrent episodes or residual depressive symptoms (American Psychiatric Association, 2010; National Institute for Health and Clinical Excellence, 2010; Spijker et al., 2013). However, resources are scarce and currently, there is limited availability of therapists to provide ongoing treatment models (Saxena, Thornicroft, Knapp, & Whiteford, 2007), although new delivery methods may widen availability. A key need in the field is research on how to increase the availability, throughout the world, of therapists proficient in providing depression specific therapies. Internet-based CT, either alone or coupled with minimal therapist support, should be studied as well as alternative prevention strategy. Recent randomized controlled trials indicate that internet based CT started after (partial) remission is effective preventing a rise in depressive symptomatology and in preventing relapse and recurrence (Holländare et al., 2011, 2013; Kok et al., 2015). In addition, using technical devices to support ongoing patient monitoring, such as text messages and apps for smart phones might facilitate long term monitoring on relapse (Bockting, Elgersma, et al., 2011; Bockting, Kok, et al., 2011; Kordy et al., 2013).

It is important to recognize that MDD is a recurrent disorder for most vulnerable individuals, and that relapse/recurrence has severe consequences. Offering CBT in the acute phase of a depressive episode (stage 2) should be considered more often, given that its prophylactic effects last beyond the end of treatment. Both continuation CT (and possibly also continuation IPT) and brief preventive CBT (Wellbeing CT, MBCT, Preventive CT) following remission (stage 3, residual stage) with other types of treatment including ADM, reduces the risk of relapse in MDD and expand the evidence-based choices for patients and practitioners. To date the evidence suggests that depressed individuals with the worst prognosis (e.g., people with a risk profile characterized by recurrent MDD, unstable remission, and possibly also early age of onset of MDD) stand to profit the most from continuation CT or preventive CBT/MBCT.

Enormous investments have been made in England to increase access to evidence based psychological interventions through the Improving Access to Psychological Therapies (IAPT) program (D. M. Clark, 2011). Early results indicate that this large-scale initiative successfully increases the availability of clinical guideline recommended psychological treatments for depression and anxiety disorders (Clark, 2011). Not only did access to these treatments improve, response to treatment improved also (Clark, 2011; Gyani, Shafran, Layard, & Clark, 2013). In contrast, there was an increase from 1998 to 2007 in treatment of MDD in outpatient with antidepressant medication in the USA, while the use of psychotherapy declined (Marcus & Olfson, 2010; Olfson et al., 2002). Studies that examine national policies and practices will lead to a better understanding of the linkage between these as aspects of public health and access to evidence-based psychological

treatments. Given that MDD is often a recurrent disorder, and with substantial consequent health care costs, the long-term clinical and economic effects of interventions that are focused on relapse and recurrence should be studied.

Finally, as the science related to the models of risk for depression advances (Dobson & Dozois, 2008), future studies should test theoretical models that may explain the high relapse and recurrence risk in longitudinal cohorts. The prescriptive indicators and mechanisms of current relapse prevention strategies require study, allow discovery of which preventive strategy is the best for whom. Relapse rates can be reduced with preventive psychological interventions, but not only relapse but also recurrence rates still remain unacceptably high. Therefore, efforts to reduce relapse and recurrence further are a high priority. The field now has effective psychological treatments that have been proven to prevent depression, much remains to be done to improve recovery rates, better understand what works for whom and ensure effective treatments are accessible.

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Conflict of interest

All other authors declare that they have no conflicts of interest.

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