CHAPTER 1

Prevalence and Risk Factors for Relapse in Major Depressive Disorder

Most individuals who have experienced prior depressive episodes are aware of their vulnerability for relapse. In this chapter I outline the prevalence estimates of MDD, the definition of relapse and recurrence in diverse settings, and risk factors for relapse and recurrence. It is important for both the clinician and the client to be aware of risk factors for relapse and recurrence.

PREVALENCE OF MDD AND RELAPSE

According to the World Health Organization (WHO), depression is the leading cause of disability and a leading risk factor for suicide, resulting in an estimated annual global loss of one million lives (WHO, n.d.). The disease burden of depression is further compounded by its significant comorbidity with other somatic and mental diseases (WHO, 2019/2021; Kupfer et al., 2012). Crossovers throughout life from anxiety disorders to MDD are also very common (73%; Craske & Stein, 2016; de Graaf et al., 2002; Lewinsohn et al., 1997).

MDD is a common mental health condition with an estimated lifetime prevalence rate ranging from 11% to 14% in a general population cohort (Steel et al., 2014; James et al., 2018). In outpatients the prevalence is markedly higher (27%; Wang et al., 2017), and in adolescents, major depressive episode (MDE) prevalence has increased from 8.1% to 15.8% in the United States between 2009 and 2019 (Daly, 2022). A recent estimate indicates that the overall prevalence rate in 27 European countries was 6.38% in 2021 (Arias-de la Torre et al., 2021). MDD is one of the leading causes of disability worldwide among all mental and somatic conditions (James et al., 2018).

Prevalence of Relapse of MDD in Different Settings

The prevalence of relapse varies depending on the specific setting, from living independently in the community to living in mental health care centers. Over a 20-year period, the relapse rates in two community cohorts (with varying numbers of previous MDD episodes) were estimated to be 35–42% (Eaton et al., 2008; Hardeveld et al., 2010; Hardeveld, Spijker, de Graaf, Hendriks, et al., 2013; Hardeveld, Spijker, de Graaf, Nolen, et al., 2013). In community cohorts, following remission or recovery from the first depressive episode of MDD, these individuals have a 40–60% increased lifetime risk of developing a subsequent MDD episode (Eaton et al., 2008; Moffitt et al., 2010).

With each episode, the risk of relapse rises by 16% as studied in a general community cohort (Hardeveld et al., 2010). Relapse rates in clinical samples treated in mental health care centers from diverse countries ranged from 45% to 75% (Maj et al., 1992; Surtees & Barkley, 1994; Kanai et al., 2003; Kennedy et al., 2003; Solomon et al., 2004; Holma et al., 2008). A lifetime relapse rate of 40% was found in a mixed study covering *persistent depressive disorder* (that is, chronic depression with a depressive episode with a duration of at least 2 years) and (nonpersistent) first-onset MDE (Mattisson et al., 2007). Within the time frame from mid-adolescence to early adulthood, 25–47% of this population will have a recurrence of MDD (Lépine & Briley, 2011; Bockting, Hollon, et al., 2015; Curry et al., 2011; Cox et al., 2012; Kovacs et al., 2016). In several randomized controlled trials including participants that had experienced two or more depressive episodes (typically individuals who receive treatment as usual), cumulative recurrence rates of 33–50% were reported within 1 year, a 64% increase in 2 years, and up to 94% in 10 years (Teasdale et al., 2000; Ma & Teasdale, 2004; Bockting et al., 2005; Bockting, 2009b; Bockting, Hollon, et al., 2015; Biesheuvel-Leliefeld et al., 2017; de Jonge et al., 2019). Cumulative recurrence rates for individuals who experienced at least three previous episodes ranged from 34% to 68% in 1 year (Kuyken et al., 2008, 2015; Bondolfi et al., 2010; Godfrin & van Heeringen, 2011; Williams et al., 2014; Huijbers et al., 2015). So, although relapse rates might differ per setting and follow-up time, relapse after remission and recovery is common in MDD across several settings, with a mean lifetime number of seven depressive episodes (Kruijshaar et al., 2005), underlining the necessity to offer effective relapse prevention intervention after remission or recovery.

RISK FACTORS FOR RELAPSE IN MDD

In order to anticipate and mitigate a potential relapse in a subsequent episode, be aware of the risk factors for relapse after remission and recovery of an *acute episode*. Below is an overview of risk factors that are identified as ones that heighten the predisposition of relapse, as studied in longitudinal studies. It's also important to inform the client and their loved ones of these risk factors. Note that for clients who are on antidepressants, not taking them regularly is a risk factor for relapse (see also Chapter 4, "PCT and Continuation of Antidepressants"). The sessions that come later in this book will give you guidance with this process of educating your clients about these risks. With this knowledge the client can make an informed decision on investing in PCT after partial and full remission and recovery.

Psychological and Stress Factors

My team and I conducted an extensive systematic review and meta-analysis of vulnerability factors derived from leading psychological models that precede depressive relapse (Brouwer et al., 2019). This extensive systematic review included 66 identified studies that assessed the potential risk factor before relapse and examined prospective relapse from 43,586 published articles. The predictive effect on subsequent relapse of MDD factors derived from five leading psychological models tested: cognitive, interacting factors with stress (*diathesis stress*), behavioral, psychodynamic, and personality models. We found no supportive evidence for factors derived from the psychodynamic model. The assumption of a diathesis stress model is that the individuals' vulnerability (due to their rigid *dysfunctional beliefs* or schemas) only contributes to heightened risk of relapse when confronted with stressors, such as *life events* (Conway et al., 2015; Ingram et al., 1998; Monroe & Simons, 1991). Cognitive-behavioral theories include the diathesis-stress assumption explicitly (Hankin & Abela, 2005; Conway et al., 2015; Ingram et al., 1998; Monroe & Simons, 1991). There were no studies published that examined the prediction of factors derived from diathesis-stress models. Nevertheless, cognitive factors by themselves were predictive for prospectively assessed relapse in a depressive episode (Brouwer et al., 2019). Vulnerability factors derived from the cognitive and personality approaches, specifically higher levels of negative attributional style (Buckman et al., 2018) and neuroticism were found to predict a heightened risk of subsequent relapse, as has been reported in other studies (e.g., Buckman et al., 2018, and Prieto-Vila et al., 2021, respectively). These results provide support for the notion that both negative personality traits and cognitive factors are related to the risk of depressive relapse, or that they both represent an underlying style that puts a person at increased risk (e.g., Brouwer et al., 2019; Forand & DeRubeis, 2014).

Demographic Factors

While MDD occurs in women twice as often as it does in men, women do not have a heightened risk for relapse in MDD as compared to men (van Loo et al., 2018; Wojnarowski et al., 2019). In an individual patient meta-analyses including participants of 14 randomized control trials (RCT) in the control groups with a variety of previous MDD-episodes comparing diverse psychological interventions, my team and I found that being married decreased the risk of relapse. Being divorced, separated, or widowed significantly increased the risk of relapse (at the level of a trend; $p < .10$) in the control group of individuals that participated in randomized controlled trials aimed to evaluate diverse relapse preventions strategies (Breedvelt et al., 2024). Other demographics (age, gender, race, employment status, education, socioeconomic status, and intelligence) have been studied as well in a meta-analysis including patients treated with cognitive-behavioral therapy, but none of these demographic factors were associated with a heightened risk of relapse in MDD (Wojnarowski et al., 2019).

Life Events, Trauma, and Stress

Stress-related risk factors that contribute to onset of the first depressive episode do not necessarily contribute to subsequent relapses. I found, in a patient sample that participated in

an RCT, that *minor stressors* (*daily hassles*, like missing your connection to the next train) predicted relapse, whereas life events (such as a divorce, the death of a loved one)—a predictor of onset—did not (Bockting, Spinhoven, Koeter, Wouters, Schene, et al., 2006). This finding could be explained by the *stress sensitization* or *kindling hypothesis*, stating that minor stressors that do not trigger the onset of depression, may trigger subsequent relapses (Kendler et al., 2000). There is indeed additional evidence that with having experiences of more depressive episodes, less stress is needed to trigger a next relapse both in adults (Post et al., 1986; Post, 1992; Kendler et al., 2000) and in adolescents (Ezquiaga et al., 1987).

However, this evidence does not fully explain why life events do not trigger relapse. Genetics may play a role in the speed of kindling (Kendler et al., 2011), suggesting that there are different pathways to relapse depending on the genetic background of the individual (Stapelberg et al., 2011). It is presumed that this kindling effect indicating that even minor stressors trigger relapse especially holds for individuals characterized with low genetic risk, whereas kindling effects do not play a role for individuals with high genetic risk (for instance with high familial prevalence of mental health conditions; Kendler et al., 2001).

A systemic review examined within mostly prospective studies found that individuals who have had a previous depressive episode predominantly triggered by life events, had fewer relapses overall than did those who had a previous depressive episode that was not triggered by prior life events (Swann et al., 1990). *Chronic stressors* (such as an ongoing family conflict or somatic illness) were found to be associated with more frequent relapse and poor outcome over time (Reno & Halaris, 1990), while acute life events were not associated (Swindle et al., 1989). Also, a depressive episode itself can result in life stressors (so-called dependent life stressors, such as marital problems), that increase the risk of a relapse (Hammen, 1991).

Childhood Trauma

To get a robust indication of the impact of childhood trauma as a risk of relapse, Nanni and colleagues (2012) conducted a systematic review and meta-analysis including 16 epidemiological studies (N = 23,544 participants). Childhood trauma was defined as physical abuse, sexual abuse, neglect, or family conflict or violence during childhood. This meta-analysis found that childhood trauma was associated with an elevated risk of developing recurrent and persistent depressive episodes (odds ratio = 2.27, 95% confidence interval [CI] = 1.80–2.87). The impact of childhood trauma on risk of relapse was examined as well in a cohort study in the Netherlands (Hovens et al., 2015). Within this longitudinal cohort study (NESDA), childhood trauma was defined as experiencing emotional neglect and/or psychological, physical, and/or sexual abuse prior to age 16. In this study, childhood life events were defined as divorce of parents, early parental loss, and being "placed in care." Childhood trauma was associated with an increased risk of first relapse. However, childhood life events did not predict relapse. In multivariate models, to sort out which factor between all the childhood trauma factors and clinical factors predicted relapse, emotional neglect was the only significant independent predictor of relapse. This effect was primarily explained by the level of depressive symptoms. In line with experiences in clinical practice, individuals with a history of childhood trauma had a higher severity of anxiety and depressive symptoms at baseline. These higher levels of (residual) symptoms by themselves increase

the risk of relapse. Even more so, a gene × childhood trauma interaction effect was found to predict relapse (Lok et al., 2013). That is, the results showed individuals with T-allele of the MTHFR gene may be at an increased risk of MDD relapse if exposed to childhood trauma (e.g., physical or sexual child abuse, the death of a parent as a child). Overall, childhood trauma, including childhood neglect, is a risk factor for relapse.

Genetic Factors

Heritability is estimated to explain about 40% of depression cases (Wray et al., 2018) and is related to multiple genes in interaction with environmental factors (Lewinsohn et al., 1998; Bockting, Hollon, et al., 2015; McHugh et al., 2013; Sharma et al., 2016; Rai et al., 2017). However, a study in adopted twins reported a far lower heritability of 16%. That is, life stressors were the strongest risk factors for depressive symptomatology, apart from parental upbringing. This is of interest, given that these adopted individuals lived in different circumstances and experienced different life stressors (Gatz et al., 1992). Also, reinforcing that environmental factors contribute more to depressive symptomatology than genetic factors was the finding that the shared (family) environment explained most depressive symptoms in young individuals (Thapar et al., 1998).

However, specific genetic loci only explained limited variance (only 2% of the variance was explained for relapse; Köhler et al., 2018). And in Mendelian randomization studies, which are used to study the causal link between genetic factors and depression, these loci explained only 1% of the difference (Sullivan et al., 2000). So, it is unclear what specific genetic factors play a role in depression and relapse. In sum, heritability does play a role in depression, although psychological, stress, and environmental factors play a far more substantial role.

Neurobiological Factors

My team and I also conducted a systematic review and meta-analysis investigating robust prospective evidence for biomarkers derived from leading neurobiological hypotheses for MDD onset and relapse. Out of 67,464 published articles, $N = 75$ were included, of which $N = 35$ studied risk factors for prospectively assessed relapse (Kennis et al., 2020). Neurobiological factors had to be assessed before onset or before relapse as well as relapse over time to be included in this meta-analysis. The factors consisted of neuroimaging, gastrointestinal factors, immunology, neurotrophic factors, neurotransmitters, hormones, and *oxidative stress*. Out of all examined factors, only a stress hormone predicted relapse of MDD with a small effect size ($N = 19$, OR = 1.294, $p = .024$). However, when controlling for already existing depressive symptomatology and statistical factors such as correction for multiple testing, even cortisol did not predict relapse. So, in sum, no evidence was found that (neuro) biological factors as assessed in clients before relapse, predicted a relapse over time.

Clinical Factors

A variety of clinical factors have been identified that increase the risk of relapse. Two clinical factors that have been consistently found to heighten risk of relapse are a history of

more previous depressive episodes and higher levels of residual depressive symptoms, after remission and recovery (e.g., Burcusa & Iacono, 2007; Piet & Hougaard, 2011; Kuyken et al., 2016; Breedvelt, Warren, et al., 2021; Breedvelt et al., 2024). For example, my team and I conducted an individual patient meta-analyses including participants of 14 RCTs in the control groups with a variety of previous MDD-episodes comparing diverse psychological interventions. We found that the higher the number of previous depressive episodes and higher level of residual depressive symptoms at baseline as measured with HAM-D increased the risk of relapse (Breedvelt et al., 2024).

Even limited residual symptoms, for instance having more concentration problems than before the onset of depression, can increase the risk of relapse (Bockting, Hollon, et al., 2015). Also, having concurrent mental health conditions (comorbidity, such as having an anxiety disorder), earlier age of onset, a more severe previous episode, and a shorter time of remission have been reported as risk factors, although not all studies have found the factors to be risk factors for relapse (Scholten et al., 2016; Buckman et al., 2018; Breedvelt, Warren, et al., 2021; Breedvelt et al., 2024).

Another individual patient meta-analysis including participants of 4 RCTs ($N = 714$) compared a psychological intervention (PCT or mindfulness-based cognitive therapy) while tapering antidepressant medication (ADM), to ADM monotherapy (Breedvelt, Warren, et al., 2021). That meta-analysis found that early age of onset, shorter duration of remission, as well as greater levels of baseline residual depression predicted increased overall risk of relapse.

Further, computational analysis of individuals participating in international RCTs on relapse prevention (Breedvelt et al., 2024; Breedvelt, Warren, et al., 2021) indicated that a combined risk score consisting of lower age of onset of depression (onset before the age of 23) and higher depression severity significantly enhances the prediction of relapse risk when compared to using only an interview to assess depression severity questionnaires.

Overall, it is important to examine the number of previous episodes and the level of residual symptoms to get an indication of a heightened risk of relapse. Identifying such heightened risk is vital for clinicians to target their treatment and indicate relapse prevention interventions as soon as the client is in remission. My team and I await the results about relapse prevention from ongoing studies in which personalized interventions for relapse preventions are given depending on the characteristics of clients (see Chapter 5, page 145 for StayFine study).

WORKING MECHANISMS OF PCT

There are some indications that PCT targets several risk factors or mechanisms, as described above, that contribute to relapse and thereby prevent relapse in depression. Examples of these risk factors include stress sensitivity, dysfunctional (cognitive) beliefs, and positive and negative emotion regulation.

My team and I found in an RCT that experiencing minor daily stressors as well as having low levels of a stress hormones, that is, morning cortisol, does increase risk of relapse, but not for the group of individuals that were randomly assigned to receive PCT (as compared to

care as usual group; Bockting, Spinhoven, Koeter, Wouters, Visser, et al., 2006). Also, in a different RCT, my team and I found that change in dysfunctional beliefs (in the group randomized to PCT versus continuation of antidepressants only) mediated reduction of relapse risk. However, the explained variance was no more than 9% (Bockting et al., 2018). A closely comparable explained variance was found in another RCT (de Jonge et al., 2015). PCT may change not the content of beliefs, but rather the thinking processes and meta cognitions; this finding was also previously reported about cognitive-behavioral therapy (Paykel et al., 1999; e.g., Teasdale et al., 2000, 2001). Findings in another RCT that used a stress task during magnetic resonance imaging before and after PCT as compared to a wait-list control group, suggest that PCT might obtain its preventive effects by changes in regulation of positive affect and positive cognitions, and that this subsequently may decrease negative affect and negative beliefs (van Tol et al., 2021). These findings indicate that through PCT, changes in positive emotion regulation result in cognitive change. In PCT this cognitive change in combination with a change in positive emotion regulation might buffer individuals against the negative effects of stress. As such PCT targets several mechanisms simultaneously and thereby results in a higher level of resilience, which is needed when encountering not only profound challenges but also daily hassles in life. Further studies are needed to specifically study how PCT contributes to sustainable preventive effects in MDD, and the interplay and timing of positive and negative emotion regulation and beliefs as working mechanisms.

SUMMARY

Here, I've discussed how PCT fosters its sustainable effects by targeting several risk factors and mechanisms, including positive emotion regulation, cognition, and stress, rather than targeting one factor. In the next chapter, I outline the rationale and supporting evidence for PCT.