INTRODUCTION

The general aims of this thesis were to gain more insight into predictors of relapse, relapse rates, and preventing relapse in patients with remitted anxiety disorders in general, and specifically in remitted patients who discontinue antidepressant medication.

Here, results from the previous chapters will be summarized, the main findings are discussed in relation to the existing literature, and clinical implications and future perspectives will be addressed. The chapter concludes with an advice for Emma.

SUMMARY OF MAIN FINDINGS

In chapter 2 we investigated recurrence rates and predictors of recurrence in participants with remitted anxiety disorders from the Netherlands Study of Depression and Anxiety (NESDA). A total of 429 participants were included. According to the Composite International Diagnostic Interview (CIDI), recurrence occurred in 23.5% of participants. There was no significant difference in recurrence rates between patients with pure and multiple anxiety disorders. In those recurring, the incidence of a new anxiety disorder (as compared to that of the recurrence of the index anxiety disorder) was common (32.7%). Putative predictors were selected from a broad range of socio-demographic, illness-related and psychosocial variables. Number of years of education, percentage of time with anxiety symptoms, percentage of time with avoidance symptoms, severity of avoidance, severity of anxiety symptoms, the use of antidepressant medication, disability, a current depressive disorder, anxiety sensitivity, neuroticism, childhood trauma, and low mastery all predicted recurrence in univariable analyses (p < 0.10). Only anxiety sensitivity (OR = 1.32, P = .04) and disability (OR = 1.45, P = .02) remained significant predictors of recurrence. Despite the inclusion of a broad range of predictors, together, these variables explained 22% of the variance of recurrence ($R^2 = .22$), suggesting that other causal factors, not included in our study, critically influence relapse. These findings show that it is difficult to predict relapse on the basis of demographic, illness-related and psychosocial variables, and that relapse occurs frequently and is diagnostically unstable.

In chapter 3 we studied the impact of diagnostic instability on recurrence rates in depression and anxiety in a NESDA sample of 656 participants with a panic disorder with or without agoraphobia, agoraphobia, social phobia, generalized anxiety disorder, major depressive disorder or dysthymia at baseline, and a subsequent
remission in the following two to four years. Recurrence rates of index disorders (diagnostically stable recurrence) and newly-arisen anxiety or depressive disorders (diagnostically unstable recurrence) were calculated over a four-year follow-up period. In total, 374 (57.0%) had a relapse within four years of reaching remission. The results show that, in anxiety disorders (n=281), the recurrence rate was more than doubled when diagnostically unstable recurrence was considered – from 23.8% with a stable recurrence, to 54.8%. In patients with depressive disorders at baseline (n=173), the recurrence rate increased from 37.6% to 49.7%, and in patients with comorbid anxiety and depressive disorders (n=202) the recurrences increased from 54.0% to 66.3%. Neglecting this diagnostic instability would cause an underestimation of the true rates of re-emerging psychopathology in anxiety disorders and depression.

In chapter 4 we discussed the clinical implications after discontinuation of AD in patients with remitted anxiety disorders, and proposed a strategy for guided discontinuation with cognitive-behavior therapy (CBT). We showed that, although a CBT intervention seems to offer a promising solution, the evidence is incomplete. Studies to date focused on depression, concerned benzodiazepines instead of AD, did not include remitted patients, or did not discontinue AD. Further, we proposed a CBT intervention to guide AD discontinuation, which targets known predictors of relapse, and applies effective elements from other prevention studies which were related to, but not specifically aimed at, relapse prevention in remitted anxiety disorder patients discontinuing AD.

Chapter 5 describes a randomized controlled trial, comparing discontinuation of AD in a CBT group relapse prevention intervention (n=42), with discontinuation of AD in care as usual (n=45), in remitted anxiety disorder patients. The primary outcome measure was relapse within 16 months. The trial was stopped on ethical grounds after an unplanned interim analysis was conducted due to observed high relapse rates. The CBT group intervention did not have a protective effect on relapse; 42% vs. 44% of the participants relapsed. In addition, it also appeared that in the 16-months follow-up period, other anxiety or depressive disorders developed in an additional 19% of the participants vs. 18% of the participants, leading to psychopathology in 62% in both conditions. Only 28% succeeded in completely discontinuing AD without a relapse during the 16 months. No independent predictors of relapse could be identified. Discontinuation of AD led to the
development of severe psychopathology and appeared not to be feasible in many cases.

In chapter 6 we describe a qualitative study (n=52) which we conducted after noticing in our RCT on AD discontinuation that it was difficult to include participants with remitted anxiety disorders who wanted to discontinue AD, while the clinical problem of patients wanting to stop AD treatment is well known. This qualitative study addressed reasons for patients with remitted anxiety or depressive disorders to refuse CBT relapse prevention interventions, as well as reasons to participate. The constant comparative method was used. Analysis of the interviews yielded five different profiles of patients. Refusers did not know about the risk in general; or they denied their own risk, although they did think that this risk applied to others; they were unable to attend due to logistical reasons; or the content of the proposed intervention did not meet their expectations. Participants regarded recurrence as a risk in general, and they also saw themselves as being at risk of recurrence; or they denied their own risk of recurrence but chose to participate anyway, because they had other pertinent reasons. To increase participation, patients should fully understand their risk of relapse, and relapse prevention should be tailor-made.

DISCUSSION OF MAIN FINDINGS

In this section, the main findings for each aim are discussed and related to existing literature. Although our main focus was on people with anxiety disorders, we also refer to relapse prevention literature on depression, because anxiety and depression are related and in some of our research, we also studied depressive disorders. Additionally, in depression, relapse prevention is more advanced than in anxiety disorders.

Relapse rates in anxiety disorders in epidemiological studies

The recurrent nature of depressive disorders, with recurrence rates of 35% in the general population and up to 85% in specialized mental health care settings, has been widespread knowledge for some time (1). However, at the time we conducted the studies on relapse rates (chapters 2 and 3) less attention had been given to research on relapse in anxiety disorders. This is also reflected in the DSM–IV and also in DSM–5 criteria for anxiety disorders, in which anxiety disorders have no classification such as ‘recurrent anxiety disorder’, as compared to ‘recurrent
depressive disorder’. Further, only few studies showed that anxiety disorders are recurrent (2–7). Also, in clinical practice, recurrence in anxiety disorders was no common knowledge among either clinicians or patients.

The results from the first prospective study we conducted (chapter 2), showed a recurrence rate of 23.5% within two years in individuals with a lifetime (but not current) anxiety disorder at baseline. The second study (chapter 3) yielded a comparable relapse rate of 23.8% in a sample that had anxiety disorders at baseline, then remitted and subsequently relapsed within six years. Previous studies had shown various but substantial relapse rates, depending on characteristics of the samples and the methods, like for example the follow-up period, co-morbidity and age. Since our research, a few more studies were published, which also confirmed relatively high recurrence rates. In the Coordinated Anxiety Learning and Management (CALM) trial (8), recurrence of anxiety was examined in 274 patients who met criteria for anxiety remission after six months of randomized treatment, with a follow-up of 18 months. A collaborative care intervention was compared with usual care in primary care. The recurrence rate after collaborative care was significantly lower (29%) as compared to (41%) usual care. However, in this study, anxiety was measured by assessing anxiety symptoms with the Brief Symptom Inventory for anxiety and somatization (BSI–12) > 6 and 50% increase from the previous rating in the previous week, rather than assessing anxiety disorders according to DSM–IV criteria. In a study by Nay et al. (9), data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) on panic disorders over a three-year period were used. The results showed that, including a subthreshold category, relapse rates were 21.2% for panic disorder and 29.7% for panic disorder with agoraphobia. All studies provide consistent evidence for the recurrent character of anxiety disorders in medium–longer and longer term, and our results from chapters 2 and 3 are in accordance with these findings.

Diagnostic instability of relapse

In our study on relapse in chapter 2, we used a broad definition of relapse to investigate whether the type of anxiety disorder remains stable when it recurs, or whether patients develop other anxiety disorders, or even depression. Since we found that patients do not only relapse into the remitted index anxiety disorder, but other anxiety disorders or depressive disorders may develop, we conducted our
study in chapter 3 in which we specifically investigated this diagnostic instability of recurrence. By including the emergence of other anxiety disorders and depressive disorders after achieving remission, a better picture of the true course of anxiety and depression could be obtained. Disregarding diagnostic instability could lead to an overly optimistic view of the prognosis of remitted anxiety disorders and too low an estimate of relapse rates.

To the best of our knowledge, this was the first study that studied this phenomenon in participants who had an anxiety disorder or Major Depressive Disorder (MDD), followed by remission. The results confirmed diagnostic instability of recurrence within and between anxiety disorders and MDD. When we compare these findings with existing literature on transitions without an intermediate remission between disorders, we notice that our findings are in line with the related research that has been conducted on this subject. In a longitudinal study by Wittchen (10), the waxing and waning of symptoms and syndromes over time was shown. Additionally, for anxiety disorders, shifts between anxiety disorders over time were found, as well as between panic disorder, panic attacks and agoraphobia (11). Switches between anxiety and depression were shown in several studies (10;12–15), as well as comorbidity of, and transitions between, anxiety and unipolar depressive disorders (16–19). Nay et al. (9) conducted a longitudinal study in the general population which showed that panic disorder and panic disorder with agoraphobia are chronic and recurrent disorders of high diagnostic/symptomatic variability over time. In a recent study by Hovenkamp et al. (20), who also investigated the NESDA sample, transitions from one anxiety disorder diagnosis to another over a period of six years were determined for each anxiety disorder diagnosis separately and for subjects with a chronic and a non-chronic course. Transitions to other anxiety disorders were high, ranging from 21% – 36%, with the highest percentage in the chronic group.

Researchers speculate on explanations for diagnostic instability. It could be hypothesized that the different anxiety disorders, and even depression, are not distinct disorders, but share a common underlying pathophysiology, consisting of overlapping genetic and environmental risk factors (21;22). Following this line of thought, anxiety and depression can be regarded as one entity with different presentations over time. Therefore, in the last decade there has been increasing discussion about the tenability of the classification system of mental disorders. Consequently, some advocate a dimensional approach, which does more justice to
these underlying common factors. Symptoms of severity and duration of anxiety and level of disability, which are shared between different disorders, seem better predictors of the course of anxiety disorders than the DSM classification system (23). However, many questions currently remain unresolved, and further research is needed.

Furthermore, although the Composite Interview Diagnostic Instrument (CIDI) interview is a highly standardized and reliable instrument for assessing mental disorders with a test–retest reliability with kappa values ranging from 0.64–0.84 for anxiety disorders (24;25), and an interrater kappa value above 0.90 for all anxiety disorders (25), there are many reasons why respondents do not always answer consistently. This could also cause bias and be of influence on the stability of CIDI diagnoses.

Our findings recommend taking diagnostic instability of recurrence into account in research and clinical practice, as long as the current classification is used, since recurrence rates will be seriously underestimated if the emergence of other psychopathology is disregarded.

Predicators of relapse in anxiety disorders in general
Since the course of anxiety disorders is heterogeneous (a substantial number of patients have a relapse at some point, but others stay remitted) (26), it is important to provide patients with useful information about the likelihood of recurrence of their anxiety disorder. Therefore, knowledge of predictors of relapse is necessary. To assess predictors, studies are needed that investigate a wide range of putative predictors which should be analyzed in multivariable regression analysis. The few existing studies examining risk factors for anxiety recurrence only have included a limited number of predictors, used more homogenous samples from RCT’s, or did not use multivariable models (3;27–35). To the best of our knowledge, at the time we conducted our study (in chapter 2), it was the first study to investigate a broad range of clinical and vulnerability factors in a large cohort study (NESDA). Our finding that several factors were univariably associated with recurrence corresponds with previous studies (2;3;27;28;30–33;36;37). In our multivariable model, only disability and anxiety sensitivity appeared to be independent predictors of recurrence.
Our finding corresponds with the role of disability in anxiety disorders as found in other studies, which show that anxiety disorders are associated with severe disability (38-41) and that disability influences the symptomatic course of anxiety disorders (42) and recurrence (29). Since disability often remains present after recovery of the anxiety disorder (43;44), it is hypothesized that disability may, to some degree, be independent of the symptomatic status of patients and can still be impaired after recovery from the anxiety disorder and cause relapse of other anxiety symptoms. Improving functioning could therefore be addressed in treatment of anxiety disorders.

The role of anxiety sensitivity as a predictor of recurrence also corroborates with previous research (3;45). Anxiety sensitivity is the fear of anxiety–related sensations, and one can imagine that if an individual remains afraid of these sensations, normal bodily sensations can easily be misinterpreted and lead to recurrence of pathological anxiety. Higher anxiety sensitivity also appears to be a premorbid vulnerability and predictive of anxiety disorders (46;47). Anxiety sensitivity can be influenced by using cognitive behavioral therapy (48;49). Previously found predictors like residual phobic avoidance, a history of childhood trauma and neuroticism (2;3;27;28;30–33;36), did not appear to be predictors in our model.

More recently, in a recent collaborative care treatment trial, the Coordinated Anxiety Learning and Management (CALM) trial (8), predictors of relapse were also investigated and they confirmed some of our findings on predictors. In this study, many putative predictors were included, and smoking, being single, anxiety sensitivity index score, functional impairment and treatment with benzodiazepines appeared to be predictive of recurrence in a multivariable model. Also, in a recent maintenance CBT relapse prevention study, residual symptoms of agoraphobia after treatment in the acute phase were independently predictive of time to relapse within 21 months (50). Thus, to date, only a few common predictors appeared to be of influence on recurrence of anxiety, and studies on this subject are scarce. Furthermore, neurobiological variables are lacking in most studies. In clinical practice, prediction algorithms are needed that include a key set of known risk factors that, in combination, are best predictive of recurrence. Yan Liu et al. (51) were the first to develop a prediction tool for the recurrence of panic disorder. This decision support tool consisted of a list of risk factors that are, in combination, best predictive of relapse and can be used by clinicians during treatment. The
algorithm had good discriminative power (C statistic = 0.7863, 95% CI: 0.7487, 0.8240).

Predictors of relapse in discontinuation of antidepressants (AD)

In our RCT, no predictors of relapse after discontinuing could be identified, although many putative predictors were analyzed. This implies that relapse after stopping AD could not be predicted by psychosocial- or illness-related variables. This may have been due to a lack of power as a consequence of stopping the RCT prematurely after an interim analysis. In previous naturalistic course studies without discontinuation of AD, a number of predictors of relapse of anxiety disorders were identified. However, these predictors varied per study and no common specific predictors of relapse have been identified as yet. Moreover, relapse as a result of discontinuation of AD may differ from relapse without AD discontinuation. Possibly, an underlying biological vulnerability of the serotonergic system makes some patients more vulnerable for relapse. For example, according to ‘the oppositional tolerance hypothesis’, continued drug treatment may cause processes that oppose the initial acute effects of a drug or of receptor alterations. When drug treatment ends, oppositional processes result in appearance of withdrawal symptoms and increased vulnerability to relapse (52;53). Therefore the question arises concerning whether AD may have an iatrogenic effect that would prevent spontaneous remission from taking place.

A limitation of investigating predictors in an RCT is that these samples are often more homogeneous than in longitudinal studies. However, in our RCT we had a relatively heterogeneous sample through the use of broad inclusion criteria.

In our RCT we did not identify independent predictors of relapse in discontinuing AD. Unfortunately, studies on outcome predictors of long-term pharmacological treatment are lacking, indicating that this research area needs substantial expansion. Sufficient knowledge on factors affecting treatment, response and relapse, including neurobiological functions, comorbidity, biomarkers, and genetic features could lead to developing predictive tools to guide discontinuation decisions in an individualized manner.
The need for guided discontinuation of antidepressants (AD)

In chapter 4 we wrote a letter to the editor to emphasize the importance of the development of relapse prevention interventions for patients with remitted anxiety disorders who want to discontinue AD. These interventions are needed because relapse rates are high and patients often do not want to continue AD long-term. Based on existing research in the field, we concluded that these interventions are lacking for anxiety disorders. Existing interventions either focus on relapse prevention in depression or are applied without discontinuation of AD. We proposed a CBT intervention, based on related interventions and studies on predictors of recurrence. Since our publication, few studies have been conducted, mainly confirming the need for relapse prevention, but approaches to prevent relapse in anxiety disorders – both with or without discontinuing AD – are still almost completely lacking. A recent meta-analysis (54) has shown that in 28 studies (n=5233), discontinuation increased odds of relapse compared to continuing AD (summary OR=3.11, 95%CI 2.48 to 3.89). These studies had a maximum follow-up of one year. No new studies on psychological interventions to prevent relapse after discontinuing AD in patients with anxiety disorders were published.

In recurrent depression however, the effect of mindfulness-based cognitive therapy (MBCT) with discontinuation of AD was investigated in a few studies, but the results were inconclusive. MBCT followed by discontinuing AD was equally effective as AD continuation alone in preventing relapse (55–57). A recent study however, in which MBCT followed by discontinuation of AD was compared with MBCT and continuation of AD, showed an increased risk of relapse in the discontinuation group (58).

Concerning psychological–relapse prevention interventions in anxiety disorders without discontinuation of AD, one study was published since we wrote the letter to the editor. In this study, the efficacy of maintenance CBT in remitted panic disorder patients with agoraphobia was investigated (50). Participants responding to acute-phase treatment were randomized to nine monthly maintenance CBT sessions (n=79) or assessment only (n=78) and followed for 12 months. Maintenance CBT was more effective in preventing relapse (relapse 5.2%) than in the control condition (relapse 18.4%). In recurrent depression, the effectiveness of psychological relapse interventions has already been proven, in contrast to within anxiety disorders. Results from a meta-analysis (twenty-five trials) on psychological relapse interventions in recurrent depression suggest a greater effectiveness of
psychological interventions to prevent recurrence compared with usual care and antidepressants (59). These findings could contribute to directing research in anxiety disorders. We can conclude that preventing recurrence in anxiety disorders is challenging and sorely needed, but little evidence exists to guide clinical practice.

Efficacy of cognitive behavior therapy (CBT) group relapse prevention interventions in discontinuation of antidepressants (AD)

The results of our RCT show that the CBT group intervention did not have a protective effect on relapse and that relapse rates were high. In our sample, 42% vs. 44% of the participants relapsed. Based on previous related small-scale studies, we anticipated that there would be a preventative effect of CBT (60;61). Not only did participants not profit from the addition of CBT, but relapse rates were also high. A meta-analysis of discontinuation studies of AD in anxiety disorders showed comparable relapse rates; 36.4% relapsed within a year (54). However, studies in the meta-analysis differ from our study, having a shorter remission time before discontinuation of AD (8–52 weeks vs. 2–4 years), and a shorter AD use (8–52 weeks vs. an average AD use of 6 years). Because our sample was relatively stable, with a longer average duration of remission and use of AD, we had expected lower relapse rates. Possibly, the duration of remission does not have an impact on relapse risk, but it is not clear whether long-term AD use makes people more or less vulnerable for relapse. Studies comparing different durations of AD use are lacking. Nevertheless, our sample may have been vulnerable, as more than two-thirds had already unsuccessfully attempted to stop AD in the past, more than 50% had had comorbid disorders in the past, and half of the participants had received psychological treatment in the past two years.

In our study, participants did not only have recurrences of their previous anxiety disorder, but also high proportions of onset of other anxiety disorders or MDD in both conditions. This implies that an average of 66% of all participants who did not have an anxiety disorder or MDD at baseline developed a mental disorder within 16 months. The emerging of new disorders of respectively 16% in the CBT group and 19% in the control group is higher than can be expected from 12-months first-incidence numbers of mental disorders of 2.5% in the general population (62). This diagnostic instability of recurrence is in line with our previous findings in chapter 3, in which we showed that in anxiety disorders the recurrence rate more than doubled when the recurrence of other anxiety disorders and MDD were included.
Furthermore, an unexpected finding was that from the 71 participants whose assessments were available, only 41% of the CBT discontinuation group and 32% of the discontinuation as usual group succeeded in completely stopping AD. The remainder of the participants only lowered their doses, stopped but restarted AD again within 16 months, or did not start discontinuing at all. This is striking, since all participants explicitly chose to participate in the study with the purpose of discontinuing AD. In studies on mindfulness and discontinuation of AD in previously depressed patients, higher adherence rates to discontinuation of 53% were found in the study by Huijbers et al. (58) and two studies by Kuyken et al. (55;56)(75% & 71%), as well as in two small studies investigating discontinuation of AD with CBT in anxiety disorder patients who were not in remission (60;61). Our lower discontinuation rates may be due to our sample in which 71.4% unsuccessfully tried to discontinue one or more times before this trial and thus may have been more afraid to discontinue, or perhaps these participants were biologically vulnerable. Further, maybe our definition of unsuccessful discontinuation was stricter, because this also includes participants that succeeded in discontinuing in the first place, but restarted within 16 months.

The high relapse rates were regardless of adherence or non-adherence, with higher relapse rates in the participants that stopped but restarted or only lowered their dose. Patients who experience (the beginning of) a relapse, likely do not start the discontinuation, or do not further lower the dosage. No matter how obvious, this is an important finding and advocates carefully monitoring patients and taking all emerging announcing symptoms seriously.

**Participation in relapse prevention interventions in depression and anxiety**

Achieving the best possible participation in psychological relapse prevention interventions can be difficult. In our RCT in Chapter 4, we had trouble recruiting participants at the outpatient clinics and through using advertisements to reach many potential participants; it was hard to motivate the targeted high-risk group to participate. Low participation also occurred in a study by Apil et al. (63), investigating the feasibility and effectiveness of a relapse prevention program for depression in older people (>55). A participation rate of only 5.7% for recruited participants (92 of 1627) and 47.8% for self-referred participants (44 of 92) was reached. Low participation in primary prevention is a well-known problem in people.
with depressive symptoms (64) or for people with non-cardiac chest pain who present themselves at the emergency room of a general hospital (65).

To improve participation rates in relapse prevention interventions for patients with remitted anxiety or depressive disorders, we investigated patients’ reasons for refusing participation in a qualitative study. We compared these with reasons for participation in relapse prevention interventions and identified profiles of participating and non-participating patients. Our findings are partly in line with previous studies but also partly different. In our study, individuals without a perceived need also chose to participate. The low response to an intervention by Van der Weele et al. (66) for people at risk of depression however, showed that only those with a perceived need and with positive expectations about the intervention agreed to participate in this intervention.

Further, an important finding was that many patients perceived themselves as being at risk, but they did not attribute this risk to themselves. This phenomenon is also known as ‘unrealistic optimism’ – the tendency to underestimate personal risks about future events (67). This finding could also be viewed in the light of the motivational stages of Prochaska et al. (68;69). This model distinguishes different motivational stages in the process towards change in which refusers can be seen as individuals who are in the pre-contemplation (not being aware of having a problem or that help could be sought) or the contemplation stage (being aware of a problem and starting to consider seeking help) and therefore not yet being prepared to seek help.

Cuijpers et al. (64) mentioned three reasons for low participation in primary prevention: participants do not consider themselves to be at risk, believe an intervention is not effective, and because of the stigma associated with depression. The first two reasons were also found in our study. Stigma, however, was not a reason for refusing participation in our study. This was probably due to the fact that most of our patients had already been, or were still patients, as opposed to people in the general community in the primary prevention studies. In the study by Apil et al. (63) the patients who were approached to participate implicitly or explicitly said that they did not want to be confronted again with the depressive period of their lives. This was not mentioned as a reason in our qualitative study.

We also noticed that some patients did not want to discontinue antidepressants in the anxiety relapse prevention, because of a fear of relapse and withdrawal
symptoms. In a study by Heida–Verbeek (70), patients continued AD due to a fear of relapse, and expressed this as being “better safe than sorry”. These reasons were also mentioned by patients in a qualitative study that determined patients’ views on discontinuing long-term SSRI use (71). Even general practitioners are often reluctant to initiate the discussion about discontinuing AD (72). Further, we asked for patients’ ideal relapse prevention. It appeared that patients want it to be conducted by an expert, not to take much time and to be flexible. These results were quite similar to the results in recent studies (73;74).

METHODOLOGICAL CONSIDERATIONS REGARDING ASSESSMENT OF MENTAL DISORDERS

The NESDA studies in chapter 2 and chapter 3, and the RCT in chapter 5, all rely on categorical outcome measures, assessed by semi-structured clinical interviews (CIDI and SCID) which are based on the DSM-IV classification system. There are some limitations to this way of measuring psychopathology.

First, there are no uniform criteria for remission with respect to the length of time without symptoms that is required for anxiety disorders and dysthymia in the DSM–IV. Remission criteria are mentioned only for MDD: full remission requires a period of at least two months in which there are no significant symptoms of depression. In the NESDA studies in chapters 2 and 3, the CIDI was used and the interviews provided one-month and six-months remission assessments. Since the CIDI interview is based on the DSM–IV criteria, no remission criteria are mentioned for anxiety disorders with regard to the duration of absence of symptoms. In the RCT in chapter 5, the SCID was used, in which the absence of symptoms for at least one month is required for remission in anxiety disorders. In our study on relapse rates and predictors in chapter 2, we decided to choose a strict remission duration of at least 6 months at baseline in order to select participants with a solid and stable remission. In chapter 3 however, we used the remission criterion of absence of symptoms for at least one month, because in this study we selected participants with a disorder at baseline, followed by remission and relapse. If we had used longer remission duration (≥ 6 months), we might have falsely considered participants with remission duration of 1–6 months at the time of the assessment as not being in remission, although the remission might have continued after the assessment. However, post-hoc analyses in our study showed that using stricter remission criteria would not have made a significant difference, since 93.4% of our
sample had a remission of at least six months duration. In other studies on recurrence of anxiety disorders, conservative criteria of eight weeks or even three months of remission were used (2;4;75).

Second, our studies were based on DSM–IV classifications. In May 2013, the DSM–5 was introduced and will is currently being implemented in research and clinical practice. An important question to consider is whether using DSM–5 criteria would have influenced our findings. A few changes could have affected our studies. The duration of the symptoms has been extended to six months for all anxiety disorders (previously, this only accounted for the generalized anxiety disorders). This would possibly have caused lower relapse rates in our NESDA studies in chapters 2 and 3, because some episodes have a shorter duration. Further, DSM–5 criteria could have caused a longer time to relapse and lower relapse rates in our RCT, because the follow–up was 12 months. In the DSM–5, agoraphobia and panic disorder are now classified as independent diagnoses. In our study, panic with agoraphobia often switches to agoraphobia and to panic without agoraphobia, although switches occurred between all anxiety disorders. Therefore, instability would have been a little lower if DSM–5 criteria were applied.

Third, in the last decade there has been a lot of discussion about the usefulness of the categorical DSM classification system. Although the DSM relies extensively on a categorical approach, but also addresses, to a lesser extent, the dimensional nature of syndromes and symptoms, clinicians and researchers suggest a dimensional approach to mental disorders. For example, two individuals with a social phobia may have quite different symptom profiles and symptom severity and they may have quite different factors contributing to the pathogenesis of symptoms. With a dimensional system, such dimensions may include continuous assessment of core symptoms and dimensional assessments that cut across different disorders. This dimensional approach may do more justice to the phenotypic heterogeneity of mental disorders which at the same time have symptoms that overlap with other mental illnesses and may presumably share some fundamental biological underpinnings. Combining categorical and dimensional approaches could be complementary and useful in understanding and treating patients with diagnostically unstable recurrences, by acknowledging the changing symptoms and recurrence of symptoms over time. Using dimensional assessments would probably have yielded lower diagnostic instability in our studies, because this way we probably would have found symptoms of different (subclinical) disorders at the
same time. With a dichotomous outcome measure, we ruled out subclinical disorders. In the end, both in research and in clinical practice, it is important to assess the fluctuation of type and severity of symptoms over time.

**CLINICAL IMPLICATIONS**

Treatment guidelines are evidence-based and aimed at optimizing treatment for patients with anxiety disorders. The evidence for treatment of anxiety disorders consists mostly of short-term treatment studies from the acute phase of the anxiety disorders. Unfortunately, there is increasing evidence for the chronic and recurrent nature of anxiety disorders (2;14;23;26), but effective long-term treatments are lacking, and a long-term perspective on treatment is missing. Guidelines do, however, pay some attention to the risk of relapse and recommend making a relapse prevention plan in the final treatment phase. Our studies contribute to the growing body of evidence, both in epidemiological studies as well as after discontinuing AD, for the recurrent nature of anxiety disorders and stress the need for research on long-term treatment strategies which are aimed at reaching ‘sustained remission’.

Until these strategies are available, clinicians and patients should be better informed about relapse rates, in order to be able to make an informed decision on choice of treatment and to make arrangements for after-treatment. Regarding choice of treatment with a long-term perspective in mind, long-term effects of CBT are rarely investigated, but reported effects are modest. Relapse rates of 55% within 2–14 years were found, and two-thirds sought treatment again (76). Treatment of panic disorders yielded a modest protective effect in the medium term (77). Also, relapse rates after long-term AD use are lacking, but a recent meta-analysis showed that, in the medium term, continuing AD (54) has lower relapse rates (16%) compared to discontinuing AD (36%).

Clinicians should also inform patients about the possible negative effects of AD use, like side-effects of AD which can endure while in remission of the anxiety disorder, and which often result in people wanting to stop taking AD (70;72). Our study on discontinuing AD also showed that the adherence to discontinuation was poor, i.e. patients did not succeed in withdrawing from the medication. Patients should be made aware of the fact that relapse risks apply to them as well. When considering CBT or AD, clinicians and patients should take all this information into
account. Therefore, with regard to considering starting AD, clinicians should advice patients: “Look before you leap”.

Most patients seem to prefer psychological treatment over medication (78), although worldwide, long-term AD use is increasing (79;80), and of these long-term users, only 10% discontinue AD each year (81). Our qualitative study in chapter 6 showed that participants want to be informed about their relapse risk during the treatment or at the end. However, with making long-term choices in mind, maybe it is better to inform patients when discussing treatment options in the beginning, because the information may influence the choice of treatment. Our study also demonstrated that even when patients are familiar with relapse risks, they underestimate their own personal risk compared with other people’s risk.

As we found in our study in chapter 2, more disability and higher anxiety sensitivity, when in a remitted state, contribute to helping identify those at the highest risk of relapse. Addressing these predictors in treatment could contribute to reducing relapse risk. CBT, aimed at decreasing anxiety sensitivity using cognitive restructuring and interoceptive exposure techniques, produces promising results (48;49). Also, improving psychosocial functioning could be part of a regular CBT program. These predictors were found for all investigated anxiety disorders and thus could be applied as a transdiagnostic intervention. Our finding that relapse is often diagnostically unstable also advocates a more transdiagnostic approach to target the shared pathology across disorders. Evidence for this approach is still limited, but promising (82).

It still remains unclear what should be done after treatment in the acute phase. Guidelines recommend making a relapse prevention plan at the end of treatment and to discuss with the patient what should be done when relapse occurs. There is some evidence for relapse prevention CBT or booster sessions after regular CBT in anxiety disorders (50;83;84), but further research is needed. The possibility to contact the therapist or to make limited low-frequent appointments to be able to act quickly when symptoms recur might mitigate relapse rates. Patients expressed a wish for flexibility and tailor-made relapse prevention in our qualitative study. With respect to AD use, continuation of AD yields lower relapse risks than discontinuing, at least in the mid-term. Patients should at least be advised to consult their general practitioner or psychiatrist when they want to discontinue, for guidance and a tapering schedule, although general practitioners appear to be reluctant to taper
AD (72). Relapse symptoms and other emerging symptoms should be monitored, especially in the first three to four months after withdrawal, since relapse is most frequent in this period. Extra attention needs to be paid to symptoms of other anxiety disorders or depression since these symptoms and disorders seem to vary over time.

To conclude then, there is still a lack of knowledge on how to prevent relapse in anxiety disorders, but clinicians have an important role in informing patients on relapse risks, making a well-considered treatment choice with a long-term perspective in mind, in setting up personal relapse prevention strategies with their patients, and making arrangements to act swiftly in case relapse occurs.

**FUTURE PERSPECTIVES**

Our studies explored new areas of relapse in anxiety disorders by investigating a broad range of predictors of recurrence and instability of recurrence, by studying the efficacy of guided discontinuation of AD, and by studying reasons for non-participation in relapse prevention. However, recurrence in anxiety disorders and relapse prevention are still areas that require a lot of attention, both in research as well as in clinical practice. The most progress can be achieved in long-term studies on relapse in AD and CBT, with long follow-up periods (at least > 2 years) and by taking diagnostic instability of relapse into account by assessing a broader range of mental disorders. Methodological issues, such as losses to follow-up and patients seeking further treatment, make long-term follow-up challenging and prone to bias. In the design of RCTs on efficacy of treatments, longer follow-up periods should be taken into account. Further, to be able to make the right choice of treatment in the acute phase, relapse rates after CBT, AD continuation and AD discontinuation should be compared.

With respect to relapse prevention, more research on relapse prevention interventions or booster sessions is needed. Compared with rather successful relapse prevention strategies in depression, anxiety research is still in its infancy.

With regard to diagnostic instability of relapse, we could think of other more transdiagnostic interventions. Also, a new approach to psychopathology – the network approach – may contribute to recognizing diagnostic instability. This approach is an alternative way of conceptualizing mental disorders in which mental
disorders arise from direct interactions between symptoms where symptoms cause each other instead of being effects of a common cause.

Furthermore, to be able to provide patients with good information on the likely course of their own disease trajectory, to allow them and their physicians to make informed choices, more knowledge on predictors is required. When physiological characteristics that may play a significant role in both disease vulnerability and in response to specific therapies are identified, a more personalized medicine can be developed.

Much research remains to be done in the future, hopefully leading to a better long-term prognosis for patients with anxiety disorders.

**CLOSING REMARKS**

Dear Emma,

At the start of this thesis I was hoping that after completion I would be able to give you and other patients a better personal advice on whether to continue or discontinue AD, your risk of relapse, and what you could do to reduce the relapse risk. Based on the results of the studies we conducted, I am afraid I have to disappoint you, because what we found may not make the decision to continue or discontinue AD any easier for you. First, the relapse prevention program we investigated to help patients discontinue AD and reduce the relapse risk did not yield the effect we had hoped for. In fact, relapse rates after discontinuation were high – 43% had a relapse within a year. Unfortunately, we could not identify characteristics that predict whether you belong to the low-risk group who can probably discontinue safely, or if you belong to the high-risk group. If you had not started AD yet, I would probably have advised you to carefully consider your options with a professional from mental health care, taking into account the severity and history of your symptoms and prior treatments. Choosing treatment with AD would probably mean long-term treatment. For now, you will have to make your own personal, well-considered decision, weighing the pros and cons of continuing or discontinuing AD. If you decide to discontinue, beware of symptoms of relapse or other anxiety or depression symptoms in the months following discontinuation. But of course, I hope you’re among the lucky ones, the slight majority who can discontinue safely. Whatever you decide, always make preparations with your doctor or therapist for quick access to help in case relapse.
occurs. I will continue my work on prevention of relapse and I hope for you and other patients that research in this field will take off and that I will be able to give you better advice in the near future.

Willemijn Scholten
REFERENCES


16 Hagnell O, Grasbeck A. Comorbidity of Anxiety and Depression in the Lundby 25–year Prospective Study: The pattern of subsequent episodes. Maser, J. D.


66 Van der Weele GM, de Jong R, de Waal MW, Spinhoven P, Rooze HA, Reis R, Assendelft WJ, Gussekloo J, van der Mast RC. Response to an unsolicited intervention offer to persons aged ≥ 75 years after screening positive for


70 Verbeek-Heida PM, Mathot EF. Better safe than sorry--why patients prefer to stop using selective serotonin reuptake inhibitor (SSRI) antidepressants but are afraid to do so: results of a qualitative study. Chronic.Illn. 2006 Jun;2(2):133–42.


Vektis. Therapietrouw Monitor (Treatment Adherence Monitor).

