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The long-term course of anxiety disorders

Hovenkamp-Hermelink, Ans

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Chapter 7

General discussion

GENERAL DISCUSSION

The research described in this thesis was centered around the question why so many anxiety disorders are characterized by a persistent course and by what factors this course is determined. Despite the multitude of studies on anxiety disorders, much is still unknown about the course over several years. This is because most of the studies in the literature were cross-sectional and retrospective (and therefore subject to recall bias). The central aim of the research in my thesis was to get more insight into the longitudinal multi-year naturalistic course of anxiety disorders and to identify the factors that are associated with this course. Important knowledge gaps with respect to stability of diagnoses, underlying mechanisms and putative predictors of the longitudinal course were addressed.

To achieve this aim, I have not only studied the course of anxiety disorders, but also the changes in severity of anxiety symptoms. Anxiety disorder diagnoses are based on the classifications of the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD) [1,2]. These classifications are mainly categorical and have limitations such as high rates of comorbidity between the different anxiety disorders and between anxiety and depressive disorders, and unclear diagnostic boundaries. Moreover, the categorical systems do not take into account symptoms that fall below the threshold in terms of number and severity, which leads to a loss of information [3–5]. These limitations of the categorical classification systems led to the recognition that the categorical classification would benefit from complementing it with dimensional elements. One way to meet the demand for a more dimensional approach is to study fluctuations in anxiety symptoms for the analysis of their course, rather than the categorically defined diagnostic categories. Anxiety symptoms are not restricted to diagnostic boundaries and are also present at the subthreshold diagnostic level [6]. Yet, they are key features of anxiety disorders, and as such changes in severity of anxiety symptoms reflect important aspects of the course of anxiety disorders. Studying both anxiety disorder diagnoses and anxiety symptoms created the possibility to approach the longitudinal course of anxiety disorders on both of these levels.

The general discussion of my thesis starts with an overview of the main findings and conclusions. These findings are arranged on the basis of the two viewpoints: severity of anxiety symptoms and course of anxiety disorders. Second, I will discuss the findings and place them in the context of existing literature. Third, I will give a reflection on the methodology used in the studies of this thesis, to provide insight into the benefits and pitfalls of these methodologies. Fourth, the potential impact of the findings for clinical practice will be outlined and recommendations for future studies will be given. I will finish with a general conclusion based on the results of the research in my thesis.

SUMMARY OF MAIN FINDINGS

Severity of anxiety symptoms: associations with cognitive factors and with chronotype (Chapters 2, 3, and 4)

Changes in the severity of anxiety symptoms were analysed and the longitudinal associations with the cognitive factors anxiety sensitivity and locus of control were examined. Furthermore, I investigated whether changes in severity of anxiety symptoms were associated with changes in chronotype.

Chapter 2

Research questions: How stable is anxiety sensitivity over a period of two years? Are changes in anxiety sensitivity associated with changes in severity of anxiety symptoms?

The psychological construct anxiety sensitivity is linked to the onset of anxiety symptoms, panic attacks and to the onset of anxiety and depressive disorders, as well as to other disorders which were formerly classified as Axis I disorders [7–10]. Anxiety sensitivity was also found to be a predictor of persistence of anxiety disorders [11]. Nevertheless, although the severity of anxiety symptoms is one of the key factors in the prognosis of anxiety and depressive disorder course trajectories, the association of anxiety sensitivity with severity of anxiety symptoms is unclear. The first aim was to test the stability of anxiety sensitivity over a two-year period. Subjects from a NESDA sample were used who were diagnosed with an anxiety disorder, a depressive disorder or both and subjects without an anxiety or depressive disorder. I found that anxiety sensitivity is relatively stable over the two-year period. Yet, a mean-level decrease was found with moderate effect size. The second aim was to analyse whether the change in anxiety sensitivity was associated with a concurrent change in severity of anxiety symptoms. In univariable and multivariable analyses I found that this longitudinal association exists. This finding that a decrease in anxiety sensitivity is associated with a decrease in severity of anxiety symptoms may imply that intervening on anxiety sensitivity may be beneficial for all subjects who are suffering from anxiety symptoms.

Chapter 3

Research questions: Is locus of control a stable personality trait? What are the bidirectional relationships between locus of control orientation, symptom levels of anxiety and depression, and life-events?

Cognitive vulnerabilities are important in the aetiology and maintenance of anxiety disorders [12,13]. One major cognitive vulnerability factor is locus of control (LOC), which reflects an individual's perception about the ability to control the personal environment and future [14,15]. LOC is usually considered to be a personality trait and therefore thought to be moderately stable over time, but as with other personality traits it was found that

LOC can change over time, especially for specific age groups or in case of specific role transitions such as parenthood [16,17]. LOC is operationalized as a unidimensional scale that runs from an external orientation (the belief that the outcomes of your life are the result of fate, luck, or chance) to an internal orientation (the belief that the outcomes of your life are the result of your own actions). Someone with an external orientation usually experiences more stress and is more prone to develop an anxiety or depressive disorder (see Chapter 3). Despite all this knowledge, little is known about the longitudinal relationships between LOC and severity of anxiety and depressive symptoms, nor about the influences of negative and positive life-events on these relationships. Such analyses require a longitudinal study design with repeated measures. The stability of LOC over nine years was investigated. In addition, the bidirectional relationships between LOC orientation, symptom levels of anxiety and depression, and positive and negative life-events were disentangled over this time period and five assessment waves. LOC was found to be rather stable over nine years. As with anxiety sensitivity, despite its stability, LOC can change; on average LOC became slightly more internally oriented during these nine years. A more external LOC, but not an internal LOC, predicted higher severity of anxiety and depressive symptoms, whereas LOC did not predict the incidence of life-events. For the reverse associations I found something remarkable. Severity of anxiety symptoms proved not to predict LOC, whereas higher severity of depressive symptoms did predict a more external LOC. Negative life-events also predicted a more external LOC, while positive life-events predicted a more internal LOC. These prospective associations between LOC and severity of anxiety and depressive symptoms indicate that processes that yield a more internally oriented LOC could alleviate the burden of anxiety and depressive symptoms.

Chapter 4

Research questions: Is chronotype a stable trait or can it change over a period of seven years? Are changes in severity of anxiety and depressive symptoms longitudinally associated with changes in chronotype?

Circadian rhythms are reflected in the concept chronotype, or an individual's preferred timing of sleep and activity. Chronotype is the expression of genetic predisposition and environmental factors [18,19] and is usually considered as a relatively stable trait-like construct [20,21]. Some prefer activities early in the day (morning types), while their counterparts (evening types) are more active later on the day and go to sleep later [21,22]. There are indications that being an evening-type is a vulnerability for developing a depression. However, the findings until now are contradictory. For anxiety, an association with chronotype has not been found. The first aim was to test the stability of chronotype over a period of seven years. The second aim was to analyse whether a longitudinal association exists between a change in severity of anxiety and depressive symptoms and a change in chronotype. The results indicate

that chronotype is moderate stable, yet can change substantially at the individual level. A longitudinal association was found between change in severity of depressive symptoms and change in chronotype, but no association was found for change in severity of anxiety symptoms and change in chronotype.

Anxiety disorders: stability of diagnoses over time and predictors of a persistent course

Chapter 5

Research questions: How stable is the diagnostic classification of anxiety disorders over time? Does this stability differ between subjects with a chronic course and subjects with a course characterized by remissions and subsequent relapses?

Subjects with a current anxiety disorder diagnosis at baseline were selected from the Netherlands Study of Depression and Anxiety (NESDA). I investigated the presence and type of anxiety disorder diagnoses after 2-, 4-, and 6-year follow-up. Transition from one anxiety disorder diagnosis to another was common and percentages ranged from 21.1% for social anxiety disorder to 46.3% for panic disorder with agoraphobia after six years of follow-up. Transition percentages were higher when subjects had a chronic anxiety disorder diagnosis compared to subjects who had remissions followed by relapses during the follow-up period. These longitudinal patterns indicate that anxiety disorder diagnoses are not stable over time. This instability of diagnoses raises the question whether the classification of the different diagnoses of anxiety disorders is sufficiently substantiated. This finding undermines the validity of the different categories of anxiety disorders. A more pronounced dimensional approach to the classification of anxiety disorders seems appropriate. This perspective is elaborated upon in more detail below in the section on the dimensional perspectives on psychopathology.

Chapter 6

Research question: What factors can be identified that predict a persistent course of anxiety disorders?

Investigations at predictors of onset of anxiety disorders have frequently been performed (see for instance [23–25]), yet there are many questions left regarding the predictors of persistent anxiety disorders. In this study I conducted a systematic literature search and reviewed studies reporting on predictors of a persistent course across the lifespan. In addition, the strength of the evidence of predictors was indicated. I found that anxiety disorder persistence was notably predicted by clinical and psychological characteristics, in particular by having panic attacks, comorbid personality disorders, recent treatment seeking, poor clinical status after treatment, higher severity and longer duration of avoidance behaviour, lower extraversion, higher anxiety sensitivity, and higher behavioural inhibition. Unlike what was found for onset of anxiety disorders, socio-economic factors could not be related to a persistent course. Based on this review, patients at risk of a

persistent anxiety disorder can be identified, which may help us to better understand anxiety disorders and improve treatment strategies. In addition, the results can be used in epidemiological longitudinal studies to further improve the knowledge of the naturalistic course of anxiety disorders.

REFLECTION ON THE MAIN FINDINGS

In this paragraph the results, as summarized above, are being discussed and placed in the context of the literature. In particular, the relevance will be discussed with respect to the following topics: dimensional or categorial approach of anxiety disorders; anxiety and depression: two sides of the same coin?; trait versus state; and predictors of a persistent course.

Dimensional or categorical

All anxiety disorders showed high transition percentages over six years follow-up. This means that a patient with a specific anxiety disorder diagnosis at intake can develop symptoms that are indicative of other anxiety disorders over time, so that the diagnosis must be replaced by a different anxiety disorder diagnosis. In addition, in previous studies it was found that diagnostic categories cannot always reliably be differentiated [26]. Co-occurrence of distinct disorders is the rule, rather than the exception and boundaries between categories are not always clear [5]. Our findings in combination with prior literature raised the question how clinically useful the distinction of separate anxiety disorder diagnoses is and whether this distinction is sufficiently valid in scientific terms. This refers to the debate about 'splitting or lumping' disorders in psychiatric diagnoses, which already began in the 60s of the last century [27] and is still ongoing. Splitters point to the heterogeneity of anxiety disorders and support the division of anxiety disorders into clearly defined categories to arrive at more homogenous patient groups. Lumpers point to the fact that similar same etiologic factors may result in multiple phenotypic outcomes; they prefer to pull together anxiety disorders, despite the different clinical manifestations. Recently other methods are suggested for stratification of psychiatric disorders, such as clustering based on data-driven methods or normative modelling to unravel the heterogeneity underlying psychiatric disorders (reviewed by [28,29]). However, whatever method is used to stratify anxiety disorders, the current categorical classification of anxiety disorders is not fully satisfying, and many believe that this requires to be supplemented with a dimensional approach.

In addition to comorbidity of the various anxiety disorders, comorbidity of anxiety and depressive disorders is also highly common [30–32]. To do justice to the commonalities as well as to the differences of anxiety and depressive disorders and to provide a more adequate description of the psychopathology of these disorders, more nuanced models

have been developed [12,33–36], which were described in more detail in the introduction section of this thesis. The Hierarchical Taxonomy Of Psychopathology (HiTOP) model [37] was developed to address the aforementioned diagnostic problems and was meant as an alternative to the current classifications of the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD) [1,2]. This HiTOP model is an interesting, well-designed model that addresses some disadvantages of the classical categorical classification. Yet, it misses other aspects (see [38]) and therefore gives the impression of a 2D photo of a 3D reality. Especially the factor time is important in this context. Symptoms of anxiety disorders may change over time, comorbidities with other disorders can develop or disappear, and one disorder can switch to one or more other disorders. The categorization of HiTOP ignores these temporal changes and with that the model does insufficiently justice to the true nature of anxiety (and other) disorders. Furthermore, such a hierarchical classification with the allocation of generalized anxiety disorder (GAD) and major depressive disorder (MDD) in one group and the other anxiety disorders in another group is not only endorsed, but also disputed.

Our studies do not provide any information as to whether GAD should be assigned to anxiety or depressive disorders, as the associations between anxiety and depressive disorders was not the subject of our research. However, Beesdo et al. [39] found that GAD has more in common with the fear anxiety disorders than with depression as to risk factors and longitudinal course types. Zbozinek et al. [40] concluded that the high comorbidity rates between anxiety and mood disorders, in particular GAD and MDD, are likely inflated because of overlapping diagnostic symptoms and the hierarchical model with the higher order factor ‘general distress’, on which GAD and MDD load. Furthermore, Hettema et al. [41] reviewed the nosologic validity of GAD and MDD. They concluded that GAD and MDD have strong overlap, yet there are also clear differences and that the relationship between GAD and MDD does not differ from the relationship between other anxiety disorders and MDD. According to these authors, distinguishing GAD and MDD as distinct psychiatric diagnoses need not to be questioned.

Another dimensional model that is developed to overcome the disadvantages of the categorical system is the Research Domain Criteria (RDoC) program of the National Institute of Mental Health (NIMH) [42,43]. The RDoC constitutes a framework that has been developed to facilitate research on psychopathology. It is aimed especially on genetic and neurobiological analyses, while the HiTOP is focused on symptoms and psychopathology. The analogy between the RDoC and HiTOP models is that they are dimensional, and they cut through the traditional boundaries of diagnoses. HiTOP and RDoC do not compete but complement each other. Besides acclaim (see [44]), RDoC also received criticism because of its focus on biologically defined units and measures, methodological doubts, and uncertainties about the extent to

which this system can supplement the DSM [45–47]. Whether the HiTOP and the RDoC models are the solution to the controversy between categorical and dimensional approaches remains currently unresolved. The discussion between a categorical or dimensional approach of mental disorders, especially anxiety and depressive disorders, has not yet been settled.

In summary, the findings of the studies in this thesis underline that a more dimensional approach of anxiety and depressive disorders is more suited to describe the nature and course of these disorders than strictly adhering to diagnostic categories and boundaries. A dimensional assessment of psychopathology makes it possible to take account of the fluctuations in severity of symptoms and changes between symptoms over time. In clinical practice, however, diagnoses of anxiety disorders are based on the current categorical classification, with the clinical diagnosis also taking into account the impact of a mental condition on personal and social functioning. Such a clinical diagnosis is still important and also practically useful for providing adequate treatment, despite its inherent problems [48]. The HiTOP and RDoC models are promising additions to the existing categorical classifications, but their significance for the clinic is still limited. The HiTOP needs further development and reconciliation before it can be introduced in the clinic. The RDoC is not meant to replace the current diagnostic classification but is especially constructed for research purposes. The significance of HiTOP and RDoC for clinical practice lies mainly in the fact that these models facilitate the translation of research findings into practice.

Anxiety and depression: two sides of the same coin?

As indicated in the previous section, comorbidity between anxiety disorders and between anxiety and depressive disorders is the rule rather than the exception. Furthermore, switching from anxiety to depression, and from depression to anxiety, occurs regularly [31,49]. Anxiety and depressive disorders share common aetiology, the genetic correlation between these disorders is high (see reviews of [50,51]), and similar neurobiological mechanisms are implicated [52]. In addition, anxiety and depressive symptoms overlap and anxiety symptoms are frequently found in depression and vice versa. Psychotropic medication, especially selective serotonin reuptake inhibitors (SSRIs), is effective in subjects who suffer from anxiety and/or depressive disorders [53]. These findings have led to a dispute whether anxiety and depressive disorders should be considered as two different entities or as different manifestations of one and the same underlying disorder [54].

The results of our studies on locus of control and chronotype show that anxiety and depressive symptoms are differently associated with both concepts. Whereas severity of depressive symptoms was predictive of the locus of control orientation, severity of anxiety symptoms had no effect on locus of control. A similar difference was found in the study of chronotype: a change in severity of anxiety symptoms had no association with a change in chronotype, while severity

of depressive symptoms had. Although anxiety and depressive symptoms cannot be used as synonyms for the corresponding disorders, the symptoms are key features of these disorders. The differential associations of anxiety and depressive symptoms with locus of control and chronotype that I found suggest that anxiety and depressive disorders are not two sides of the same coin. This view has already been suggested in the literature. In these previous studies differences were reported between the two disorders with regard to risk factors for their onset [55]; response mechanisms to SSRIs [53]; and neural systems [56]. An explanation for the many commonalities and differences between anxiety and depressive disorders could be that both disorders share a common 'core' component, or a latent variable underlying both disorders, as was suggested by, for example, Blanco et al. [57] and Mansell and McEvoy [58]. In addition to this common factor, both disorders have their own unique characteristics, responsible for the differences. This view is supported by the results in my thesis on locus of control and chronotype.

Trait versus state

Trait and state concepts are intertwined, and the question arises whether a distinction between both concepts can be made clearly. Personality traits are considered to be relatively stable during lifetime, while state concepts are considered to be momentary and affected by the situation [59]. In our studies of locus of control (LOC), anxiety sensitivity (AS), and chronotype, usually considered as traits or trait-like concepts, the rather high rank-order consistencies found fit in with the trait concepts, but at the same time the mean-levels changed over time. In addition, the stability estimates of LOC, AS, and chronotype equalled the stability estimates of severity of anxiety and depressive symptoms, which are more state-like concepts. In addition, in compliance with state concepts, LOC was affected by the situation, more specifically by intermediate life-events: having experienced more negative life-events predicted a more external LOC, more positive life-events predicted a more internal LOC. This clear influence of situational factors together with the comparable stability estimates of the trait-like concepts LOC, AS, and chronotype, and the state-like concepts anxiety and depressive symptom severity show that traits are not static concepts, but can change and are more dynamical than is often thought. This supports the set-point theory of Ormel et al. [60], which says that personality traits can respond to environmental influences. Following this theory, LOC, AS, and chronotype might change due to experienced life-events (experience-dependent set-point model) or these concepts have a stable component supplemented with a component that responds to life-events (mixed set-point model).

Predictors of a persistent course

The systematic review revealed that especially clinical and psychological characteristics constitute predictors of a persistent course of anxiety disorders. The findings of this review can be used to identify patients at risk of a poor prognosis and may help us to better understand anxiety disorders, improve treatment strategies, and inform future studies.

Nevertheless, there are some issues that require attention. First, an existing association does not always imply a causal relationship. Second, the question whether and how psychotropic medication influences the course of anxiety disorders requires a well-designed clinical trial and third, predictors of a course with a switch from an anxiety to a depressive disorder require investigation too. Special attention should be given to the mechanisms by which psychological vulnerabilities exert their influence on the longitudinal course of anxiety disorders. The results of this systematic review indicated that psychological vulnerabilities may play a key role in the course of anxiety disorders. At the same time, many subjects with high psychological vulnerabilities do not develop anxiety disorders nor persistent course trajectories. Additional research is needed to eliminate this inconsistency. Despite these remaining questions, the results of this review reveal that a multicausal perspective on the naturalistic course of anxiety disorders is important which fits in well with the plea in the previous paragraph for a more dimensional approach of anxiety disorders. This multicausal view has been further elaborated by Jeronimus [61] in the dynamical systems perspective. This perspective indicates that anxiety and depressive disorders develop in an environment where dynamic interactions between affective, cognitive, and behavioural aspects influence emotions, mood, and personality. These processes can result in anxiety and depressive disorders. However, how these dynamic processes affect these disorders over the course of time remains to be investigated.

METHODOLOGICAL CONSIDERATIONS

Study designs and methodology

All empirical studies, except the systematic review of Chapter 6, were based on data from the Netherlands Study of Depression and Anxiety (NESDA). The NESDA study design has several strengths, such as the large number of subjects; the inclusion of a high number of individuals with a current or a history of anxiety or depressive disorders and healthy controls, by which is meant that they have no current anxiety or depressive symptoms or disorders nor a history of it [62]; and the relatively low attrition despite the 12-year follow-up with repeated measurement waves [63]. These characteristics make the NESDA study very useful and effective for studying longitudinal research questions. Yet, the NESDA study has some limitations that one should keep in mind when interpreting the results. First, although attrition is relatively low (13% after 2-years of follow-up), there are some determinants associated with attrition: younger age, lower education, not being of North European descent, recruitment place Amsterdam, no previous participation in research, and having major depressive disorder (MDD). Also subjects with comorbid anxiety-depressive disorders and with higher symptom severity were more prone to drop out of the study [63]. This selective attrition may limit the generalizability of the outcomes and may have led to

a sample where individuals with the most severe pathology are not included. Second, at baseline no inclusions were allowed of people with a primary diagnosis of a psychiatric disorder that could affect the course trajectories of anxiety and depressive disorders, such as a bipolar disorder, obsessive compulsive disorder, or severe addiction disorder [62]. Third, most of the NESDA data were collected by means of interviews or self-reporting questionnaires. These methods are proven to be highly reliable, but it cannot be excluded that there was some information bias [64]. Fourth, the repeated assessment waves are effective in detecting changes over time, but the time periods between the measurements were relatively long (two or three years), which means that interim developments may have been missed. Finally, the studies of this thesis were observational. Despite the usefulness of observational studies to identify relationships between variables and outcomes, there is a caveat on causality. To establish causal relationships experimental studies are recommended (see [65]). Nevertheless, despite these limitations, NESDA is a unique sample that provides ample opportunities to study the course of anxiety disorders.

Observational cohort studies, that is the repeated measurement and analysis of data from the same group of people, have important advantages compared to cross-sectional studies, such as the possibility to investigate developments over time and the examination of multiple outcomes [66]. The analysis of longitudinal data, however, requires special statistical techniques which enable us to analyse changes in explanatory variables or predictors and relate these changes to outcome variables. One disadvantage is that outcomes at group-level cannot be automatically translated to the individual level. An important aspect that plays a role here is that the variance within individuals is three to four times larger than at group level, according to Fisher et al. [67]. Nevertheless, research at the group level remains relevant. Knowledge about differences between people is just as important as knowledge about differences within people. The individual and group level study designs have both advantages and disadvantages. It depends on the research question which study design is most suitable [68]. If an individual study design is preferred, then the single-case experimental design (SCED) could be an interesting method [69].

For the *systematic review* (Chapter 6), I chose to focus solely on studies on trajectories of patients with diagnosed anxiety disorders, not on anxiety symptoms. The use of categorical diagnoses has large clinical utility. For instance, making a clear distinction between individuals with and without disorder diagnosis can inform the clinician who will and will not benefit from treatment, which can improve the implementation of effective interventions. Yet, the choice to include exclusively studies on anxiety disorders may have led to incorrect exclusion of studies that analysed anxiety symptoms. A focus on the trajectories of anxiety symptoms would have given the opportunity to take account of subthreshold anxiety disorders and comorbidity. However, at the same time my a priori selection criteria prevented bias because

studies that were not initially designed to analyse the course of anxiety disorders were excluded. Furthermore, there was a large heterogeneity in study designs and methodologies of the included studies. One aspect that should be mentioned here is the lack of a clear definition in the literature of the concept of 'persistent anxiety', due to different definitions of remission, recovery, relapse, recurrence and the different time frames used to define these concepts. To handle this issue, I have defined a persistent course as having an anxiety disorder diagnosis at both baseline and follow-up, but I do realize that this is only one approach of the concept of persistence. In addition, a persistent anxiety disorder can be either a chronic course or an intermittent course with remissions and relapses. There are indications that individuals of these two course types differ in the severity of anxiety symptoms and predictors of onset. In addition, some anxiety disorders are more likely to have a chronic course, whereas other anxiety disorders more often have an intermittent course [70–72]. However, I found insufficient information to substantiate this difference in course types for all anxiety disorder diagnoses, and therefore I merged both course types and treat them as one persistent course in the analysis. Future studies could separately analyse predictors of a chronic course and of an intermittent course, which may reveal more detailed information about factors related to these two course types.

In the studies reviewed, different statistical techniques were used to assess predictors of anxiety disorder persistence, but also there were large differences in the type and number of anxiety disorders studied. Some studies focused on a single anxiety disorder (e.g., panic disorder, or generalized anxiety disorder), two, three, or a range of anxiety disorders, or used the general term anxiety disorder without further specification. An additional uncertainty factor is formed by the different analysis methods that are used. Kempe et al. [73] found that logistic regression can give different results when using different time frames. In the studies of this systematic review the follow-up periods differed substantially with a range from two to twelve years. It seems indicated to perform additional analyses with different time frames to identify predictors of anxiety disorder persistence. In case the longitudinal course is an intermittent course with remissions and subsequent relapses, a recurrent events analysis seems to be more suited to analyse predictors, as this method showed to be more stable than logistic regression [73]. The statistical analysis methods used in the selected studies varied from frequencies, chi-square tests, analysis of variances, linear mixed model analysis, and different kinds of regression analyses (Cox proportional hazards regression analyses, hierarchical stepwise regressions, multivariable, multivariate and multinomial logistic regression analyses). There is no information whether the unstable outcomes of logistic regression due to a restriction to a specific time point also applies to other statistical techniques. It is highly desirable that future studies investigate the influence of time frames on the reliability of the prediction methodology. In this way, these statistical techniques can be improved even further, thereby increasing the evidence of the identified predictors.

Repeated measurements

To analyse the repeated measurements data of the multiple assessment waves I used statistical techniques intended for correlated data. In this case generalized estimating equations analysis (GEE) and structural equation modeling (SEM). The use of GEE and SEM gave us information about how anxiety symptoms change over time and what factors can be associated with these changes over the same time period. GEE uses the mean and the variance to estimate population-averaged regression coefficients [74,75]. A limitation of GEE is the requirement of large sample sizes, but this requirement was met by the use of the large NESDA sample. Another limitation is that the interpretation of the regression coefficients of GEE can be less easy. These coefficients combine the between-subjects and within-subjects relationships and they are not standardized. Furthermore, GEE does not provide in a goodness-of-fit test of the model. [74]. Yet, GEE has some clear advantages. GEE enabled us to analyse non-normally distributed data; excluding cases with missing data was not necessary as GEE can handle missing values; and time-invariant as well as time-varying covariates could be analysed. Like GEE, structural equation modeling (SEM) also handles correlated data well. SEM is a data-analytic technique with several appealing advantages [76,77]. As I did not study latent variables, but direct and indirect associations between observed variables instead, our SEM analyses can be seen as path analyses. SEM allows for testing associations of all variables at different time points simultaneously. Variables can be predictor and outcome at the same time. Direct and indirect effects of one variable on another could be shown. This procedure prevented the use of several separate analyses. Other advantages of SEM were that missing data could be handled, model fit could be determined, and the path diagram from the SEM model could be displayed visually. Yet, SEM also has some methodological limitations. Multicollinearity between the variables is a common problem in regression analysis [78]. It can bias the results of SEM analysis, but unfortunately, there is no simple way to detect and correct for multicollinearity [79]. In the study of locus of control, none of the variables were so highly correlated that there was multicollinearity, according to the correlations which were all lower than 0.80 (see Field [80]). Because of this, I do not think that multicollinearity was an important complicating factor in our SEM analyses. Another limitation is that I cannot rule out the possibility that I have omitted variables that were not available but that are relevant to the model and might have affected the parameter estimates [77,81]. Despite these limitations of GEE and SEM, these techniques enabled us to obtain insight into the relationships between cognitive factors or chronotype on the one hand and changing severity of anxiety symptoms on the other.

CLINICAL IMPLICATIONS AND FUTURE RESEARCH

There are various treatment options for anxiety disorders, consisting of either psychological therapy or pharmacotherapy or a combination of both. Treatment is often effective in achieving a remission or reducing the severity of anxiety symptoms and with that it improves the quality of life (see review of Bandelow et al. [82]). Nevertheless, in many patients, the anxiety disorder is characterized by a persistent course. It is remarkable that treatment guidelines still take little account of this persistent nature. For instance, in the guidelines of the Netherlands Trimbos-institute [83] only one sentence is devoted to the chronicity of anxiety disorders and no specific treatment options are provided. In contrast, the same guidelines of the Trimbos-institute for depressive disorders [84] have an entire chapter on chronicity and treatment resistant depression, in addition to a chapter on prevention of relapse. Clinicians should acknowledge the often persistent course of the complex, dimensional anxiety disorders and tailor the treatment accordingly.

One aspect that should be addressed in future research on the longitudinal course of anxiety disorders is the role of the panic attack specifier. In the DSM-5 severity specifiers were added to classify the diagnoses [85,86]. The *anxious distress specifier* is applied to major depressive (MDD) and bipolar disorders. In NESDA studies it was shown that the anxious distress specifier predicts persistent MDD as well as poorer treatment outcomes [87,88]. The *panic attack specifier* on the other hand is applicable to all psychiatric disorders [1]. Nevertheless, so far, there is hardly any literature describing the significance and predictive value of the panic attack specifier for the individual psychiatric disorders. Consequently, the significance and clinical utility for anxiety disorders is also unclear. There is only one study that examined the panic attack specifier. Allan et al. [89] investigated in patients with a social anxiety disorder (SAD) the effect of the panic attack specifier on symptom severity and comorbidity of other psychiatric diagnoses. They found that patients with panic attack specifier had elevated somatic anxiety symptoms compared to patients without this specifier. No other differences between the two groups were found. It must be noted that sample size was modest (SAD without panic attack specifier: n = 52; SAD with panic attack specifier: n = 14). Additional research into panic attack specifier may indicate whether and to what extent this specifier also predicts the longitudinal course of anxiety disorders.

Although not part of this thesis, I would like to mention the issue of prevention. To reduce the risk to develop an anxiety disorder, sufficient attention should be paid to prevention programs. These programs should start early in life, as onset of anxiety disorders is often in childhood, adolescence, or early adulthood [90,91]. The importance of prevention early in life is confirmed by a recently published large international study of the World Mental Health Surveys [92]. This study found that specific phobia with an onset in childhood is

related to more comorbidity, persistence and severity of internalizing disorders including anxiety disorders throughout life. Negative experiences in childhood in combination with a sense of low personal control [35] are circumstances that can mediate the onset of anxiety disorders. If untreated, the anxiety disorders tend to become persistent and co-occurrence of other psychiatric and somatic disorders is relatively common [91]. Unfortunately, there is a dearth of literature on prevention strategies especially in children (see also [93]). There are some studies who indicate that prevention programs in children are efficacious in preventing developing anxiety disorders [94,95]. Yet, more research is required to get a more complete picture of the vulnerabilities to anxiety disorders, and to set up evidence-based prevention programs.

I have not been able to investigate the effect of treatment on the course of anxiety disorders, as all studies in this thesis were observational. Until now there is no good overview of the effect and efficacy of treatment, either psychotherapy, pharmacotherapy, or combined, on the course of anxiety disorders over several years. Bandelow et al. [96] performed a review of treatments of anxiety disorders but were not able to indicate the effect of treatment on the long-term course. They indicated that there are hardly any controlled studies on treatment periods over 12 months. Besides, in a meta-analysis Cuijpers et al. [97] found evidence that for panic disorder, but not for social anxiety disorder and generalized anxiety disorder, a combination of psychotherapy and antidepressant medication is more effective than either of these treatments alone. This effect of combined therapy lasted for two years. Yet, as time to first remission is 16 months (pure anxiety disorders) to 24 months (comorbid anxiety-depressive disorders) [49], this result does not indicate whether treatment is effective in anxiety disorders that persist beyond two years. Thorough clinical research, for instance by means of randomized clinical trials, is required to elucidate the long-term efficacy of psychotherapy and pharmacotherapy in patients with persistent anxiety disorders. Clearly, such studies would be complex and costly, and it would not be easy to acquire the funding needed for such projects. As a second-best option, analysing large databases of patients in regular treatment over time (e.g. Routine Outcome Monitoring) could be helpful to acquire better knowledge on these issues. Examples of such large databases are the IMPROVE project, which combines data from several sources to support the optimal treatment choices [98], and the TRacking Adolescents' Individual Lives Survey (TRAILS), a large cohort study that follows the development of children towards adulthood [99].

A special recommendation for future research on longitudinal patterns of anxiety disorders is to explore the potential of specific symptom profiles instead of anxiety disorder diagnoses. The use of symptom profiles better reflects the dimensional nature of mental disorders. Analysing symptoms instead of disorders provides the possibility to take into account sub-threshold symptoms, severity of symptoms, and changes in severity of symptoms over time,

which is ignored in the case of a categorical approach (see [3,98,99]. If anxiety symptoms are used for research, the complex aetiology as outlined by Kendler and Gardner [100] must be taken into account. In their study it was found that the aetiology of symptoms involves two causal pathways: first, a temporally stable pathway defined by genetic and early environmental factors which are mediated by personality, particularly neuroticism; second, an occasion-specific pathway defined by genetic risk factors and childhood adversities, followed by recent stressful life-events mediated through episodes of MDD or GAD. The results of this thesis fit in well with this etiologic model, as we found that recently experienced life events influence anxiety symptoms (see Chapter 3). In addition, the etiologic model of Kendler and Gardner [100] underlines the aforementioned recommendation to investigate the role of psychological vulnerabilities in the longitudinal course over years. However, how the complex aetiology described by Kendler and Gardner [100] is related to persistent anxiety disorders is unknown yet.

CONCLUSIONS

In this thesis I have investigated different aspects of the natural longitudinal course of anxiety disorders. The research was conducted from two different perspectives, aimed at either the anxiety disorder diagnoses or at changes in severity of symptoms. Anxiety disorder diagnoses are highly instable over time and several factors that can influence the course, either concurrently with anxiety symptom severity or as predictor of anxiety disorders or symptoms, were identified. The validity of a categorical classification of different anxiety disorders is debatable. Once someone is diagnosed with an anxiety disorder, it is mainly clinical and psychological characteristics that predict whether the course will be persistent or not. The studies on anxiety symptom severity revealed that cognitive factors, that is external locus of control and anxiety sensitivity, are less static than is generally assumed and influence the severity of anxiety symptoms and thereby the course over time.

In conclusion, anxiety disorders do not represent a set of well-defined separate entities, nor do they belong to a unitary, discrete entity with clearly defined causes. Instead, anxiety disorders are complex dynamical systems with respect to distinctive and shared symptoms, comorbidities, aetiology, and changes of symptoms and diagnoses over time. Consequently, a dimensional approach to anxiety disorders fits better than a categorical one to describe the psychopathology and classification. The findings of this thesis increased the knowledge about the longitudinal course of anxiety disorders and thus partially fill the gaps in the literature. Furthermore, this thesis provides many leads for follow-up studies into the longitudinal course of anxiety disorders, for which recommendations are given above. Although the research described in this thesis is far from complete, the results can contribute

to a better understanding of anxiety disorder patients and their suffering. Moreover, the findings may contribute to recognizing patients with a poor prognosis. Future studies into the longitudinal course of anxiety disorders can build on the results of this thesis and find ways to improve the prognosis of individuals with a persistent anxiety disorder.

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