Chapter 1

General introduction and thesis outline

1.1 Epidemiology of commonly occurring anxiety disorders

Anxiety disorders are characterised by strong feelings of fear and distress that are often accompanied by physical sensations. They incur significant suffering and affect the individual's level of functioning. Anxiety disorders are the most frequently occurring psychiatric disorders, with an estimated 12-month prevalence of 12.0% in the European adult general population (Wittchen et al., 2011), and 10.1% in the Netherlands (de Graaf et al., 2012). Anxiety disorders occur across all ages and are far more prevalent in women than in men: for women, lifetime prevalence estimates range from 16.3% (Wittchen et al., 2011) to 23.4% (de Graaf et al., 2012), while for men lifetime prevalence estimates range from 7.8% (Wittchen et al., 2011) to 15.9% (de Graaf et al., 2012). The Diagnostic Statistical Manual, fourth edition, text revision[1] (DSM-IV-TR, American Psychiatric Association, 2000) defines several subtypes of anxiety disorders: panic disorder with or without agoraphobia (PD/A), agoraphobia without panic (AP), social phobia (SP), generalised anxiety disorder (GAD), post-traumatic stress disorder, obsessive compulsive disorder, specific phobia, acute stress disorder, anxiety disorder due to medical condition, substance-induced anxiety disorder, and anxiety disorder not otherwise specified. Following a common approach (Penninx et al., 2008; Bruce et al., 2005), this thesis focuses on PD/A, AP, SP, and GAD. These four disorders commonly result in referral to mental health care (Bijl & Ravelli, 2000), they share many features, and differ with regard to aetiology, expression, and clinical course from the other anxiety disorders (Friedman et al., 2011; Stein et al., 2010; Lebeau et al., 2010).

PD/A is characterised by repeated episodes of intense fear, which are accompanied by physical symptoms (for example increased heart rate, sweating, trembling, shortness of breath, chest pain, nausea, faintness, paraesthesia, or hot or cold rushes), feelings of derealisation, fear of losing control or of dying. In addition to worry about recurrence of the attacks and possible (physical) consequences of the attacks, there are behavioural changes in response to the attacks. In PD/A, panic attacks can occur with or without symptoms of AP. In SP, a strong and constant fear of social situations or situations in which one is subject to judgement by others is central. The places or situations that incur fear are avoided, as when the individual is exposed to them he or she fears this leads to extreme anxiety and possibly panic attacks. Individuals with GAD experience prolonged and constant uncontrollable fear and/or worry about everyday life. This fear is accompanied by restlessness, tiredness, concentration problems, irritability, increased muscle tension, or sleep difficulties. For the general population, 12-month prevalence estimates for PD/A range between 2.3% (Wittchen et

[1] In 2013 DSM-IV-TR was replaced by DSM-5, this led to a number of changes which are described in box 1.1.

Box 1.1 Changes in DSM-5 anxiety disorder

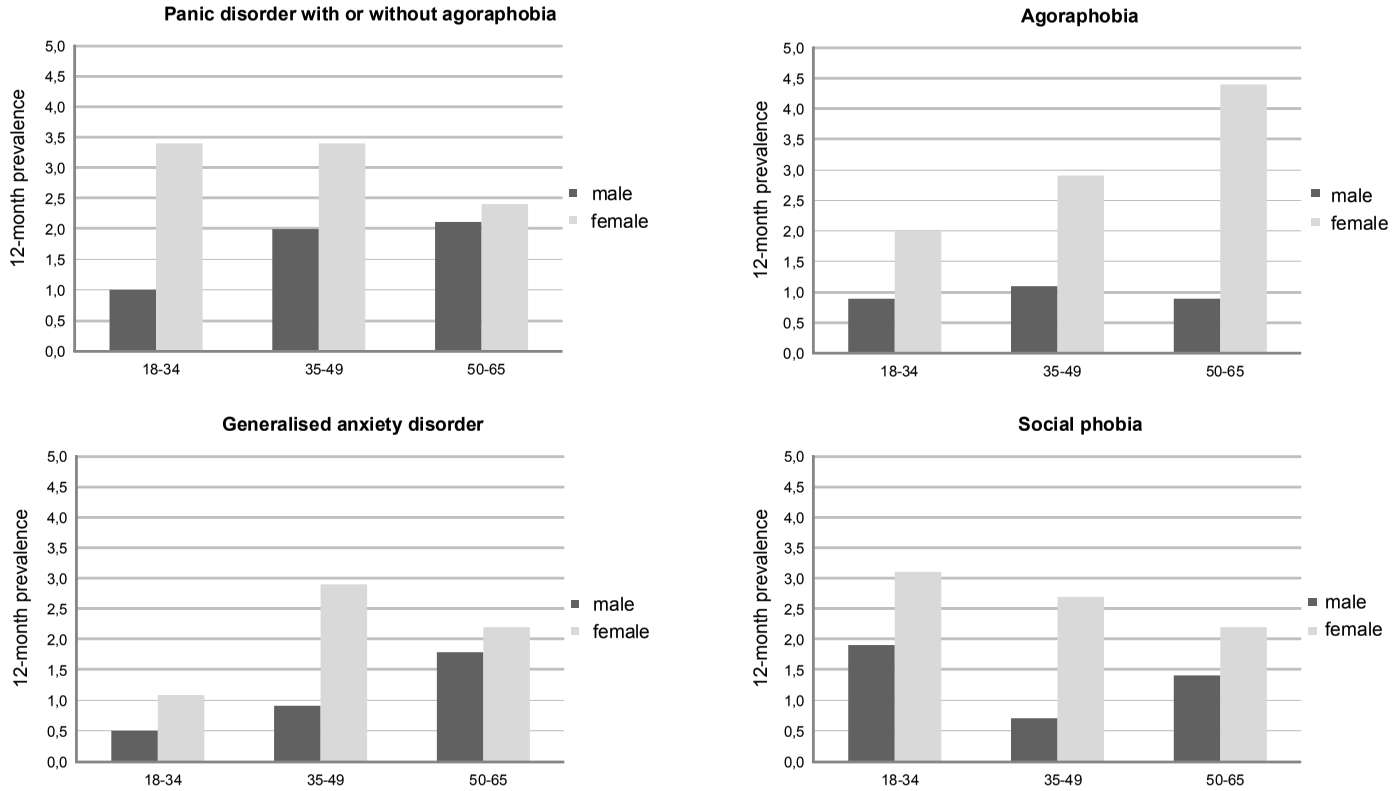
In 2013 DSM-IV-TR was replaced by DSM-5. This led to a number of changes in the anxiety disorder category. Obsessive compulsive disorder is no longer categorised under anxiety disorders but has instead been moved to the chapter obsessive compulsive and related disorders. Post-traumatic stress disorder and acute stress disorder are no longer categorised under anxiety disorders but have been moved to trauma- and stress related disorders. It is no longer necessary for an individual to recognise their fear is unreasonable or extreme to meet diagnostic criteria for social anxiety disorder (social phobia) or specific phobia. Instead, it must be recognised that the fear is disproportional in relation to the actual threat. For all age groups minimal duration of symptoms is set at six months. Panic attacks can be noted as a specification in any DSM-5 disorder. The diagnoses of panic disorder and agoraphobia are no longer connected, DSM-5 simply contains panic disorder and agoraphobia as separate diagnoses each with its own criteria. The specification generalised has been removed from social anxiety and stage fright has been added. Separation anxiety and selective mutism have been added (American Psychiatric Association, 2000).

al., 2011) and 1.2 (de Graaf et al., 2012). For AP prevalence estimates range between 2.0% (Wittchen et al., 2011) and 0.4% (de Graaf et al., 2012). For SP they range between 2.0% (Wittchen et al., 2011) and 3.8% (de Graaf et al., 2012), and finally, for GAD, prevalence estimates range between 1.5% (Wittchen et al., 2011) and 1.7% (de Graaf et al., 2012). Figure 1.1 shows the 12-month prevalence of PD/A, AP, SP, and GAD in the European adult general population, specified by gender and age group.

Anxiety disorders generally have an onset in adolescence or early adulthood (Baldwin et al., 2010). Although for different anxiety disorders, typical ages of onset have been described, these onsets tend to overlap, and have broad ranges: PD/A and AP often have adolescent- through mid-adult onset (Beesdo et al., 2009; Kessler et al., 2007; Thyer et al., 1985; Craske, 1999). SP typically has a childhood- or adolescent onset (Beesdo et al., 2009; Kessler et al., 2007; Thyer et al., 1985; Craske, 1999; Scheibe & Albus, 1992). Finally, for GAD, adolescent and early adult (Beesdo et al., 2009; Scheibe & Albus, 1992), as well as mid- (Kessler et al., 2007; Thyer et al., 1985), and late-adult onsets are reported (Craske, 1999). In addition to this early onset, anxiety disorders frequently have a chronic course. This was demonstrated by a general population study in The Netherlands, in which 47.1% of those with PD/A, AP, SP and/or GAD, and 51.7% of those with comorbid anxiety and depression, met diagnostic criteria at 7-year follow-up (Rhebergen et al., 2011). In addition, 46.5% of those with anxiety disorder, and 43.3% of those with comorbid anxiety and depression at baseline had not been free of anxiety symptoms at any point during follow-up (Rhebergen et al., 2011). On top of anxiety disorders having an early onset and a chronic course, individuals with anxiety disorders often meet diagnostic criteria for multiple anxiety disorders (inter-anxiety or homotypic comorbidity;

Beesdo et al. 2009). For example, individuals with SP are 3.8 times more likely to experience lifetime GAD and 4.8 times more likely to have PD/A than those without SP; individuals with PD/A are even 12.3 times more likely to have lifetime GAD than those who do not have PD/A (Michael et al., 2007). In addition, anxiety disorders are often comorbid with other mental disorders, such as mood-, somatoform-, alcohol abuse-, or substance abuse disorders (heterotypic comorbidity; Michael et al., 2007). Lifetime comorbidity rates range between 81% in SP to 92% in PD (Michael et al., 2007). In a general population study on comorbid anxiety and mood disorders, it was found that mood disorders often arose secondary (de Graaf et al., 2012). As such, anxiety disorders have been suggested to predispose towards mood disorders. Overall, anxiety disorders have detrimental consequences at an individual level. They are associated with severe impairment of quality of life. In 2010, anxiety disorders were the sixth leading global cause of disability in terms of years of life lived with disability (Baxter et al., 2014). In addition, although anxiety disorders are not regarded as a direct underlying cause of death according to the International Classification of Diseases and Related Health Problems (ICD), a study of the global burden of anxiety disorders concluded that 7% of all suicide mortality could be attributed to anxiety disorders (Baxter et al., 2014). A general population study showed that 60.6% of those who reported suicidal ideation had one or more anxiety disorders (Kessler et al., 2005). Among those who had attempted to commit suicide, the percentage of respondents meeting diagnostic criteria for anxiety disorders was even higher, at 70.4% (Kessler et al., 2005). These numbers signify that suicidality in anxiety is an important topic that must not be overlooked. Finally, consequences of anxiety disorders can be expressed at a societal level. Taking into account direct healthcare- (e.g. treatment), indirect healthcare- (e.g. social work), and indirect costs (e.g. productivity loss due to work absence), the financial impact of anxiety disorders was estimated at €74.4 billion for Europe in 2010 (Gustavsson et al., 2011). In the Netherlands for 2003 (based on health care consumption in 1997), the average annual excess costs of PD/A were estimated at €185 million, costs of AP were estimated at €78 million, costs of SP were estimated at €88 million, and costs for GAD were estimated at €11 million (Penninx et al., 2008). This shows that anxiety disorders have a large economic impact. Table 1.1 shows healthcare use ratios for individuals meeting diagnostic criteria of PD/A, AP, SP, and GAD relative to individuals without an anxiety disorder in The Netherlands.

Figure 1.1 12-Month prevalence of panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia, and generalised anxiety disorder.



Source: based on Wittchen, H.U. and Jacobi, F. (2005) Size and Burden of mental disorders in Europe- a critical review and appraisal of 27 studies. European Neuropsychopharmacology, 15, 357-376.

Table 1.1 12-month DSM-III-R anxiety diagnoses as predictors for care use in the past 12 months

	Primary care		Mental health care		Informal care		Any type of care	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
PD/A	4.35	2.70-7.01	3.63	2.33-5.65	1.57	NS	5.03	3.26-7.77
AP	3.34	2.00-5.56	2.61	1.30-5.26	1.93	NS	1.65	1.16-2.33
SP	1.37	NS	1.19	NS	1.49	NS	1.65	1.16-2.33
GAD	4.23	2.14-8.38	3.34	1.61-6.91	2.65	1.40-5.00	4.83	2.40-9.72
No disorder	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	

Source: based on Bijl, R.V. & Ravelli, A. (2000) Psychiatric morbidity, service use, and the need for care in the general population: Results of The Netherlands Mental Health Survey and Incidence Study. American Journal of Public Health, 19(4) 602-607. Odds Ratio's for health care utilisation are given for panic disorder with or without agoraphobia, agoraphobia without panic, social phobia and generalised anxiety disorder relative to no DSM-III-R disorder. PD/A denotes panic disorder with or without agoraphobia, AP denotes agoraphobia without panic, SP denotes social phobia, GAD denotes generalised anxiety disorder, OR denotes Odds Ratio, 95% CI denotes 95% confidence interval, NS denotes not specified, ref. denotes reference category.

1.2 The need for clinical epidemiological studies of commonly occurring anxiety disorders

In summary, anxiety disorders have a high prevalence, an early onset and chronic course, high risk for comorbidity and other adverse outcomes, and severe impact on quality of life as well as an economic impact. Taken together, this stresses the need for research on anxiety disorders that will help improve treatment through the identification of patients who are at risk for higher severity, complications, or chronicity. However, although anxiety disorders have been studied extensively, the majority of studies were randomised clinical trials (RCT's), or general population epidemiological studies. Although RCT's are well suited for studying the comparative effectiveness of new treatment options and have high internal validity, trials are often expensive, unpractical, have short term follow-up periods, demand strict protocol adherence and, have low external validity (Black, 1996; van der Lem et al., 2011; Rothwell, 2005; Vandenbroucke, 2008; Rochon et al., 2005). This entails that results from RCT's may have limited relevance for clinical practice, as populations and circumstances differ significantly. General population studies on the other hand, have few exclusion criteria. However, generalizability of findings from general population studies to clinical settings may be equally debatable (Kessler, 2007). It was estimated that in Europe, only 26.1% of those in the general population who met diagnostic criteria for any anxiety disorder received some type of formal healthcare (Wittchen et al., 2011). In The Netherlands, 31.9% of those in the general population who met diagnostic criteria for an anxiety disorder consulted primary care, 18.4%

used ambulatory mental healthcare, and 1.6% used residential mental healthcare (Bijl & Ravelli, 2000). This demonstrates that the group of anxiety disorder patients receiving mental healthcare represents only a proportion of the anxiety disorder subjects in the general population. The large group of patients not receiving help warrants studies of precursors of disorders, unmet treatment need and development of untreated disorders, a goal for which general population epidemiological studies are uniquely suited. However, when it comes to the study of factors that may be relevant tor treatment, it is likely that findings from studies in the general population may not be readily generalizable to patients in clinical practice, as these patients represent only a subset of the subjects with anxiety disorders in the general population.

Although studies with a clinical epidemiological approach, such as the Harvard Brown Anxiety Research Programme (HARP; Bruce et al., 2005), and the Netherlands Epidemiological Study of Anxiety and Depression (NESDA; Penninx et al., 2008) do exist, the samples included in these studies and those seen in everyday clinical practice may still differ to some extent (Kessler, 2007). First of all, patients who agree to take part and stay enrolled in a long-term ongoing study are likely to be more motivated and compliant than the average patient seen in clinical practice. Second, patients included in the HARP study were recruited from tertiary care facilities, which implies severity in these patients was higher than in general mental healthcare (Kessler, 2007). Conversely, NESDA patients were for a large part recruited in the general population and in primary care, implying lower severity than in general mental healthcare. Therefore:

> Clinical epidemiological studies are needed to study the predictors of individual differences in treatment response. This type of work would ideally involve investigating baseline (i.e. as of the onset of treatment) predictors of course of illness in broadly representative clinical samples (Kessler, 2007, p10).

1.3 Central aims of this thesis

In summary, anxiety disorders are highly prevalent, have a detrimental course, a high disease burden, and come with substantial societal costs. There is a strong need for clinical epidemiological studies in a naturalistic setting to describe commonly occurring anxiety disorders in individuals who present in clinical practice. The aim of this thesis is to describe the phenomenology and course of anxiety disorders in a naturalistic outpatient setting. We will outline patient characteristics and evaluate their direct clinical significance and their relevance to clinical course. Findings will be more likely to be generalizable to clinical practice, and will help clinicians identify patients who may have special needs or who are at risk for adverse outcome.

1.4 Routine Outcome Monitoring as an instrument in this thesis

At Rivierduinen, a Dutch mental healthcare provider in the greater Leiden area and at the department of psychiatry of the Leiden University Medical Centre (LUMC), patients complete an extensive battery of self-report and observer-rated measures at intake, and repeatedly during treatment as part of standard care. This procedure is known as Routine Outcome Monitoring (ROM). A more detailed description of ROM in Leiden can be found in box 1.2 and in De Beurs et al. (2011). In Rivierduinen and the department of psychiatry of the LUMC, ROM was implemented as part of standard care for patients who presented with mood, anxiety, or somatoform disorders in 2004. The primary goal of ROM is to improve care by informing clinicians and patients on diagnosis, symptomatology, and progression at intake and during the course of treatment. Although participation in ROM is voluntary, inclusion was shown to be high: in a random sample an estimated 80% of all patients was assessed at intake (De Beurs et al., 2011; van Noorden et al., 2011; Zitman, 2012). In ROM both generic and disorder-specific questionnaires are administered by trained psychiatric nurses and through supervised computerized self-report, which prevents missing data within questionnaires. Data collection covers measures of social demographics, psychiatric diagnosis, generic symptom severity, disorder-specific symptom severity, and generic health. Taking into account the setting, the extensiveness of the data collection, and the high inclusion, ROM presents a unique opportunity to undertake clinical epidemiological research in a naturalistic setting. To this end, ROM data have been anonymised and their use in scientific research was approved by the Ethical Review Board at the LUMC.

Box 1.2 ROM in the Leiden University Medical Centre and Rivierduinen

In spring 2002, the regional mental healthcare provider Rivierduinen (an institute serving a region with more than 1 million inhabitants) and the Department of Psychiatry of the Leiden University Medical Centre (LUMC) started collaboration for routine assessment of Diagnostic Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) diagnoses as well as symptom severity, wellbeing, and generic health status at intake and follow-up. This project is known as Routine Outcome Monitoring (ROM). Initially, ROM was restricted to patients who were referred for treatment of mood, anxiety, and/or somatoform (MAS) disorders. These patients form a relatively homogenous group with substantial mutual comorbidity (Kessler et al., 1996) who mainly receive outpatient care. To be eligible, patients must have sufficient mastery of the Dutch language, and have to be able to complete self-report questionnaires. Patients who are considered (by their clinician) to be too ill to complete questionnaires or refuse assessment, are excluded from ROM.

Patients are assessed by psychiatric research nurses who have been extensively trained and supervised. Assessments are scheduled at intake, at three- to four-month intervals during follow-

Box 1.2 ROM in the Leiden University Medical Centre and Rivierduinen (continued)

up, at the start of a new treatment step, and at the end of treatment. During the first session, a standardised diagnostic interview (the Mini-International Neuropsychiatric Interview-plus, MINI-plus; Sheehan et al., 1998) is administered to determine DSM-IV-TR axis-I diagnoses. In addition, socio-demographic characteristics are assessed and maladaptive personality traits are identified with the Dimensional Assessment of Personality Pathology Short Form (DAPP-SF; Livesley & Jackson, 2006). At baseline and at follow-up, a number of self-report as well as observer-rated generic and disorders specific symptom severity scales are administered in order to monitor change in symptom reduction, wellbeing, and general functioning (Sperry et al., 1996). All instruments are commonly used in treatment-outcome research and have good psychometric properties as demonstrated by national and international publications. An overview of instruments used is available at lumc.nl/psychiatry/rom-instruments. To date, treatment information has not been documented in ROM.

Results are summarised in a report which is discussed with the patient by the clinician and which is used to evaluate treatment. In addition, data are anonymised and used for scientific research. As data collection is integrated in standard care and data are anonymised, patients are not required to provide informed consent. The use of the anonymised data for scientific purposes has been approved by the Medical Ethical Committee of the LUMC.

Source: Based on Van Noorden, 2012, On real-world patients and real-world outcomes: The Leiden Routine Outcome Monitoring Study in patients with mood, anxiety and somatoform disorders; p22. With permission from the author.

1.5 Outline of this thesis

In this thesis, several studies that were undertaken to describe the phenomenology of common anxiety disorders in clinical practice are discussed. **Chapter two** describes the age of onset of commonly occurring anxiety disorders (PD/A, AP, SP, and GAD). While generally thought to be clinically relevant (e.g. associated with higher severity or more comorbidity), definitions of early onset of these disorders vary. Therefore, we used cluster analysis to define early onset based on frequency distributions of ages of onset for PD/A, AP, SP, and GAD sampled in the general population (Netherlands Mental health Survey and Incidence Study-2; NEMESIS-2).[2] To test the hypothesis that early onset was associated with higher severity, these cut-offs for early onset were then used to compare psychiatric comorbidity and general wellbeing among those with early- versus late onset anxiety disorders, both in the general population and in an outpatient sample (ROM). **Chapter three** focuses on the characteristics of adult outpatients with anxiety disorders in three different age groups (18-25; 26-45; 46-65). In this explorative

[2] In chapter two, in addition to data collected with ROM, data collected in The Netherlands Mental health Survey and Incidence Study-2 have been used. This study is described in box 1.3.

study, a comparison between age groups was made with regard to a number of social demographic factors: gender, education level, employment, and living situation. In addition, comparisons with regard to diagnostic characteristics were made to determine if differences with regard to anxiety diagnoses, comorbid substance abuse or dependence, comorbid alcohol abuse or dependence, and comorbid dysthymic or major depressive disorder existed. Finally, the three age groups were compared with regard to anxiety symptom profile, general psychiatric symptom profile, and generic health status. In **chapter four**, prognostic factors in the course of anxiety disorders were identified. We used up to 2 years of naturalistic follow-up data to explore what baseline patient characteristics were associated with response to treatment. In **chapter five** we sought to evaluate prognostic factors in the course of suicidal ideation in anxious and/or depressed outpatients. Up to 2 years of naturalistic follow-up data were analysed to simultaneously evaluate a broad set of prognostic factors that were previously associated with remission of suicidal ideation. **Chapter six** expands on measurement scales for anxiety severity, by comparing self-report and observer-rated anxiety severity instruments. We described the overall level of concordance between both types of measures in a sample of outpatients with anxiety disorders. Subsequently, patients were categorized as concordant (agreement across both types of scales) or discordant (disagreement between both types of scales), and compared with regard to social demographic, clinical, and functional characteristics in order to identify correlates of concordance. Finally, in **chapter seven**, results described in the previous chapters are summarised. General relevance to literature and clinical implications will be discussed. Strengths and limitations of the study and of using clinical data in research will be considered, and finally directions for future research will be addressed.

Box 1.3 The Netherlands Mental Health and Incidence Study-2

The Netherlands Mental health Survey and Incidence Study-2 (NEMESIS-2) is a large epidemiologic survey in the Dutch general population ages 18-64. The first wave ran between November 2007 and July 2009, the response percentage was 65% and the sample adequately represented the Dutch population (de Graaf et al., 2012). In this study, 6646 respondents with sufficient command of the Dutch language were included through a multistage random sampling procedure, sampling one respondent per household by selecting the person with the most recent birthday. Structured interviews screening for psychiatric disorders were conducted during house visits by trained- and supervised lay-interviewers. Respondents provided written informed consent, and the study design was approved by the METIGG, a national mental healthcare ethics committee in The Netherlands. A more detailed description of the NEMESIS-2 design can be found in De Graaf et al. (2010).

Source: Based on De Graaf, R. et al., (2010) The Netherlands Mental health Survey and Incidence Study-2 (NEMESIS-2): design and methods. International Journal Of Methods in Psychiatric Research, 19(3):125-141.

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