CHAPTER 1

GENERAL
INTRODUCTION
Depressive and anxiety disorders as well as alcohol use disorders are among the most common psychiatric disorders in the general population and frequently co-occur. Persons with this comorbid condition suffer from more severe impairment, more suicidality and poorer treatment outcomes than persons with either depressive/anxiety disorders or alcohol use disorders. The main objective of this thesis is to improve our understanding of the comorbidity of depressive/anxiety disorders and alcohol use disorders. How often do these disorders co-occur? What is the performance of a screening instrument for detecting alcohol use disorders in depressed/anxious persons? Which etiological pathways are involved in the development of this comorbid condition? And what are its consequences for the course of depressive/anxiety disorders as well as alcohol use disorders?

**Depressive and anxiety disorders**

Depressive and anxiety disorders are highly prevalent in the general population (World Health Organization, 2001, 2003) with lifetime prevalence rates as high as 20.0% and 18.5%, respectively, in the Dutch population (De Graaf et al., 2010). A recent review (Wittchen et al., 2011) has estimated that every year 14.0% of the total European Union population suffers from anxiety disorders and the rate for major depressive disorder is 6.9%. Both disorders have a serious impact on a person’s physical, social and occupational functioning (Judd et al., 2000; Hoffman et al., 2008; Ormel et al., 2008) and constitute a large economic burden to society (Cassano and Fava, 2002; Lopez et al., 2006; Hoffman et al., 2008). Although previous epidemiological studies have often focused on either (pure) depressive disorders or (pure) anxiety disorders, strikingly high levels of comorbidity have been reported across these disorders. Of all depressed persons, around 60% also have an anxiety disorder, and similar prevalence rates have been observed for a depressive disorder in persons with an anxiety disorder (Kessler et al., 2005; Kaufman and Charney, 2000; Kendler et al., 1993a). The present thesis therefore focuses on the mixed group of depressed and/or anxious persons and will explicitly examine the role of type and severity of depressive and/or anxiety disorders in the comorbidity with alcohol use disorders.

In this thesis, depressive disorders include major depressive disorder and dysthymic disorder according to the fourth edition of the Diagnostic and Statistical Manual of mental disorders (DSM-IV; American Psychiatric Association, 1994). *Major depressive disorder* is characterized by depressed mood and/or loss of interest and pleasure in normally enjoyable activities for at least two weeks in combination with other symptoms such as changes in appetite and weight, changes in sleep and activity, lack of energy, feelings of guilt, problems with thinking and making decisions, and recurring thoughts of death or suicide. The symptoms of a *dysthymic disorder* are less severe than those of a major depressive disorder but are chronically present over a time period of at least two years.

In addition, we distinguish the following DSM-IV anxiety disorders: generalized anxiety disorder, social phobia, panic disorder, and agoraphobia. *Generalized anxiety disorder* encompasses feelings of anxiety and excessive worry about everyday events
or activities for at least six months. The worry is difficult to control and is associated
with at least three symptoms such as muscle tension, irritability, difficulty sleeping and
restlessness. Social phobia is characterized by a persistent fear or avoidance of social or
performance situations in which embarrassment may occur. Panic disorder involves the
spontaneous, unexpected occurrence of panic attacks. Agoraphobia is characterized by
an intense fear of being alone in public places, especially in situations from which it is
difficult to escape or situations that are potentially embarrassing, or where help is not
readily available.

**Alcohol use disorders**

Extensive knowledge exists on the harmful effects of excessive alcohol use on a person’s
physical health, including cardiovascular disease (e.g., Corrao et al., 2000), cancer (e.g.,
Bagnardi et al., 2001; Boffetta and Hashibe, 2006) and neurological disorders (e.g., Taki
et al., 2006). Mental health is also affected by excessive alcohol use, which is emphasized
by the inclusion of two types of alcohol use disorders in the DSM-IV: alcohol abuse and
alcohol dependence (American Psychiatric Association, 1994). Both disorders are highly
prevalent in the general population (i.e., lifetime prevalence rates of 17.8% for alcohol
abuse and 12.5% for alcohol dependence in the United States; Hasin et al., 2007) and
constitute an important public health burden worldwide (World Health Organization,
2001, 2003; Wittchen et al., 2011).

*Alcohol abuse* is characterized by a maladaptive pattern of alcohol use leading
to clinically significant impairment or distress as manifested by at least one of the following
problems occurring within a 12-month period: 1) failure to fulfill major role obligations,
2) recurrent alcohol use in situations in which it is physically hazardous, 3) recurrent legal
problems, or 4) persistent social or interpersonal problems. For *alcohol dependence*, it is
necessary to meet at least three of the following criteria within the same period of 12
months: 1) alcohol tolerance, 2) alcohol withdrawal or withdrawal avoidance, 3) drinking
more or longer than was intended, 4) persistent desire or unsuccessful attempts to quit
or reduce drinking, 5) great deal of time spent drinking or recovering from the effects
of alcohol, 6) giving up or reducing occupational, social and/or recreational activities to
drink, 7) continued drinking despite physical or psychological problems that are likely
to have been caused or exacerbated by alcohol use. The DSM-IV criteria define alcohol
abuse and alcohol dependence as two separate and hierarchical disorders with alcohol
dependence taking precedence over alcohol abuse if criteria for both are met.

Previous studies have shown excellent reliability and validity for alcohol
dependence, but the reliability and validity of alcohol abuse are lower and more variable
(Hasin, 2003; Hasin et al., 2006). In many cases persons with a DSM-IV diagnosis of alcohol
abuse are low level drinkers, show minimal or no impairments and the stability of the
diagnosis is very low (De Bruijn et al., 2005, 2006). These findings raise the question
whether alcohol abuse, as diagnosed by the current diagnostic criteria of DSM-IV, should
be considered a genuine psychiatric disorder. This thesis aims to extend this knowledge
by separately examining the association of alcohol abuse versus alcohol dependence
with depressive/anxiety disorders. Recent studies have shown that most abuse and dependence criteria form a single latent dimension, with abuse and dependence criteria interspersed across an underlying severity spectrum (Kahler and Strong, 2006; Martin et al., 2006; Saha et al., 2006; Keyes et al., 2010; Shmulewitz et al., 2010). Moreover, the simple count of criteria forms a linear dimension (Hasin and Beseler, 2009; Dawson et al., 2010; Dawson and Grant, 2010), which has motivated us to also consider this measure of alcohol use disorder severity as a more informative phenotype.

Comorbidity of depressive/anxiety disorders and alcohol use disorders

High comorbidity rates of depressive/anxiety disorders and alcohol use disorders have been reported in cross-sectional studies in the general population (e.g., Kessler et al., 1997; Merikangas et al., 1998; Burns and Teesson, 2002; De Graaf et al., 2002a; Hasin et al., 2005, 2007) as well as in clinical samples (e.g., Lynskey, 1998; Cox et al., 1990). However, these studies are mainly based on homogeneous samples of persons with either (pure) depressive disorders or (pure) anxiety disorders. As comorbidity rates of depressive and anxiety disorders are strikingly high (around 60%; Kessler et al., 2005; Kaufman and Charney, 2000; Kendler et al., 1993a), this thesis will examine the prevalence of alcohol use disorders in a heterogeneous sample distinguishing persons with a pure depressive disorder, persons with a pure anxiety disorder and persons with both a depressive and an anxiety disorder. In addition, we distinguished alcohol abuse from alcohol dependence as these conditions might have differential associations with depressive/anxiety disorders.

Screening for alcohol use disorders

Although alcohol use disorders are highly prevalent in persons with depressive/anxiety disorders, these conditions often remain unrecognized in general psychiatric and somatic settings (Cleary et al., 1988; Rydon et al., 1992). We will therefore explore the performance of the Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 1992; Saunders et al., 1993), as a time-efficient screening instrument, in detecting alcohol use disorders in a population of depressed/anxious persons. Accurate identification of alcohol use disorders has the potential to greatly enhance health care as it gives clinicians the opportunity to offer more suitable therapy for an existing alcohol use disorder.

Possible pathways to comorbidity

The high comorbidity of depressive/anxiety disorders and alcohol use disorders is alarming as it has been linked to more severe impairments (Burns and Teesson, 2002), suicidality (Cornelius et al., 1995; Sokero et al., 2003) and poorer treatment outcomes (Burns et al., 2005). In order to optimize prevention and treatment strategies for this highly disabling comorbid condition, it is crucial to unravel the etiological pathways to comorbidity. Two types of models have been hypothesized to explain the development of comorbidity: 1) two causal models in which one disorder induces the onset of the other and vice versa, and 2) a shared vulnerability model in which common vulnerability factors independently cause the onset of both disorders.
According to a causal model, depressive/anxiety disorders may induce the onset of alcohol use disorders. This phenomenon is often explained by the ‘self-medication hypothesis’ suggesting that depressed/anxious persons misuse alcohol to reduce their distressing symptoms and, consequently, have an increased risk of developing an alcohol use disorder (Quitkin et al., 1972; Bolton et al., 2006, 2009). In contrast, the comorbidity of disorders may also be explained by a causal model considering the opposite direction: alcohol use disorders inducing the onset of depressive/anxiety disorders. In this model, depressive/anxiety disorders may be caused by interpersonal and social problems that are often observed in alcohol use disorders (Swendsen and Merikangas, 2000). In addition, alcohol may pharmaceutically induce the onset of depressive/anxiety disorders (Falk et al., 2008), for example, through dysregulation of physiological stress systems such as the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system. This thesis will therefore examine whether alcohol use and alcohol use disorders are linked to dysregulation of these stress systems.

Findings of previous studies testing these causal models of comorbidity have been inconclusive. For example, prospective studies about the first-incidence of alcohol use disorders have found positive (e.g., Marquenie et al., 2007), mixed (e.g., Kushner et al., 1999) and no (e.g., Crum and Pratt, 2001) associations for depressive/anxiety disorders as predictors. Similarly, inconsistent findings have been reported on the role of alcohol use disorders as predictors of first-incident depressive/anxiety disorders (e.g., Rohde et al., 2001 for positive findings; Grant et al., 2009 for negative findings). Some of these inconsistent findings can be explained by the heterogeneity of depressive/anxiety disorders and alcohol use disorders. For example, findings of cross-sectional studies have suggested that the association with alcohol use disorders is conditional on the status (remitted versus current disorders), type (specific disorders) and/or severity of depressive/anxiety disorders (Gilman and Abraham, 2001; Kushner et al., 2011). In addition, it may be essential to distinguish alcohol abuse and alcohol dependence, since both conditions differ in their cross-sectional association with depressive/anxiety disorders (Kessler et al., 1997; Hasin et al., 2007). Recent studies have also emphasized the importance of using severity measures for alcohol use disorders (Hasin and Beseler, 2009; Dawson and Grant, 2010). To address these gaps in literature, the present thesis will explicitly examine the role of the heterogeneity of disorders in the onset of comorbidity.

According to the shared vulnerability model, common genetic and environmental risk factors may independently cause the onset of depressive/anxiety disorders and alcohol use disorders and, consequently, explain their comorbidity (e.g., Kendler et al., 1993b; Prescott et al., 2000). This thesis will therefore prospectively examine the role of a positive family history of depressive/anxiety disorders and alcohol use disorders as well as childhood trauma in predicting first-incidence of depressive/anxiety disorders and alcohol use disorders. In addition, we will examine the role of personality traits as a shared or unique vulnerability mainly resulting from genetics and (early) environmental experiences. Previous studies have suggested that negative emotionality, a trait involving a tendency to experience negative emotional states, is of
key importance for the onset of depressive/anxiety disorders (e.g., Kennedy et al., 1998; Bienvenu et al., 2001; De Graaf et al., 2002; Spinhoven et al., 2009), whereas impulsivity, a heterogeneous construct involving traits such as disinhibition and thrill and adventure seeking, has strong links with alcohol use disorders (e.g., Clark, 2005; Krueger 2005; Acton and Zodda, 2005; Dick et al., 2010). We will explore the role of these traits in the comorbid condition of depressive/anxiety disorders with alcohol use disorders.

The role of other risk factors
In addition to depressive/anxiety disorders and alcohol use disorders, other risk factors may play an important role in the development of comorbidity. Previous cross-sectional studies have linked sociodemographics (e.g., gender, age and education; Burns and Teesson, 2002; de Graaf et al., 2002a; Marquenie et al., 2007) or general vulnerability factors (e.g., family history, childhood trauma, personality and other social factors; De Graaf et al., 2002a; Schade et al., 2004) to the comorbid condition of depressive/anxiety disorders and alcohol use disorders. In addition, depression/anxiety-related factors such as the use of antidepressant/anxiolytic medication (Rae et al., 2002; Schade et al., 2004) and addiction-related factors such as the presence of other addictive behaviors (Kessler et al., 1997; Hasin et al., 2007; Hasin and Beseler, 2009; Dawson and Grant, 2010) are possible risk indicators for the co-occurrence of depressive/anxiety disorders and alcohol use disorders. However, prospective studies simultaneously examining a large set of potential risk factors have been lacking. Therefore, this thesis will determine which potential risk factors are independent predictors of the onset of comorbidity.

Consequences of comorbidity
Prospective studies examining the effects of comorbidity on the course (i.e., persistence or recurrence) of disorders are rare and have shown conflicting results. For example, some studies have shown that comorbid alcohol use disorders predicted an unfavorable course of depressive/anxiety disorders (Mueller et al., 1994; Bruce et al., 2005), whereas others did not find such an association (Kushner et al., 1999). Similarly, comorbid depressive/anxiety disorders were a significant predictor of a poor course of alcohol use disorders in some studies (Greenfield et al., 1998; Hasin et al., 2002; Kushner et al., 2005), but not in other studies (Kushner et al., 1999; Moos and Moos, 2006; Dawson et al., 2007). Again, the heterogeneity of disorders might explain these inconsistent findings. In addition, much is still unclear about the role of other factors in predicting the course of disorders. This thesis will study the effects of comorbidity on the course of disorders while considering the heterogeneity as well as the effects of other risk factors.

Studies used in this thesis
To examine the comorbidity of depressive/anxiety disorders and alcohol use disorders, data for the current thesis are derived from two longitudinal cohort studies.
Netherlands Study of Depression and Anxiety (NESDA)
NESDA is an ongoing cohort study aimed at examining the course and consequences of depressive and anxiety disorders in the adult (18-65 years) population. A total of 2,981 persons were included at the baseline assessment in 2004-2007, consisting of healthy controls (22%), persons with a prior history (21%), and persons with a current depressive and/or anxiety disorder (57%). To represent various settings and stages of psychopathology, persons were recruited from the community (19%), primary care (54%) and outpatient mental health care services (27%). Persons with insufficient command of the Dutch language or a primary clinical diagnosis of a bipolar disorder, obsessive compulsive disorder, severe substance use disorder, psychotic disorder or organic psychiatric disorder, as reported by them or their mental health practitioner, were excluded. During a four-hour baseline assessment, extensive information was collected about the presence of psychiatric disorders and demographic, psychosocial, clinical and biological characteristics using face-to-face interviews and paper-and-pencil questionnaires (Penninx et al., 2008). Until now, follow-up assessments are conducted after two-year follow-up (response: n=2,596, 87.1%; Lamers et al., 2011) and four-year follow-up (response: n=2,402, 80.6%).

National Epidemiological Survey on Alcohol and Related Conditions (NESARC)
NESARC surveyed a representative sample of the adult (≥18 years) civilian population in the United States (Grant et al., 2001; Grant et al., 2007), residing in household and group quarters, oversampling black and Hispanic people and young adults aged 18-24 years, with data adjusted for oversampling and household- and person-level non-response. The weighted data were then adjusted to represent the U.S. civilian population based on data from the 2000 census. A total of 43,093 participants were included at the baseline interview in 2001-2002. Excluding respondents ineligible for the three-year follow-up interview because they were deceased (n=1,403), deported, mentally or physically impaired (n=781) or on active duty in the armed forces throughout the follow-up period (n=950), the response rate at follow-up was 86.7%, reflecting 34,653 completed interviews. Both assessments included a face-to-face interview assessing extensive information on psychiatric disorders as well as demographic, psychosocial and clinical information.

Aims and outline of this thesis
The main objective of this thesis is to enhance our understanding of the comorbidity of depressive/anxiety disorders and alcohol use disorders. First, we examine comorbidity patterns of alcohol use disorders in depressed/anxious persons (Chapter 2) and explore the accuracy of the AUDIT in detecting alcohol use disorders in this specific population (Chapter 3). Then, we focus on the mechanisms that are involved in the development of this comorbid condition (Chapters 4 to Chapter 7). In the last two empirical chapters, we determine the effect of comorbidity on the course of alcohol use disorders (Chapter 8) and on depressive/anxiety disorders (Chapter 9).
• Chapter 2 is based on baseline data of NESDA and examines the cross-sectional comorbidity and risk indicators of alcohol use disorders in persons with depressive/anxiety disorders. In addition, this study retrospectively examines the temporal sequencing of disorders and determines risk indicators that are specific for primary alcohol use disorders (i.e., alcohol use disorders preceding depressive/anxiety disorders) versus secondary alcohol use disorders (i.e., alcohol use disorders following the onset of depressive/anxiety disorders).

• Chapter 3 focuses on the performance of the Alcohol Use Disorders Identification Test (AUDIT), a screening instrument for alcohol use disorders, in detecting alcohol abuse and alcohol dependence in depressed/anxious persons as well as healthy controls. Analyses are based on baseline data of NESDA.

• Chapter 4 is based on baseline as well as two-year and four-year follow-up data of NESDA. In this chapter, we examine whether depressive/anxiety disorders at baseline predict first-incidence of alcohol use disorders during four-year follow-up, while considering the heterogeneity of disorders as well as the effects of other potential risk factors such as sociodemographics, general vulnerability factors and addiction-related factors.

• Chapter 5 focuses on the role of alcohol use disorder severity in the prediction of first-incidence of depressive disorders after three-year follow-up. NESARC data are used, taking into account the effects of sociodemographics, general vulnerability factors, psychiatric comorbidity and subthreshold depressive symptoms. The findings of our study also contribute to the current discussion about the introduction of severity subtypes in the definition of alcohol use disorders in the upcoming fifth edition of the DSM (DSM-5).

• Chapter 6 examines whether alcohol use and alcohol dependence are associated with dysregulation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system using baseline NESDA data. These physiological stress systems may be underlying mechanisms associating alcohol use and alcohol dependence with various psychological, physiological and behavioral problems such as depressive/anxiety disorders.

• Chapter 7 explores the role of personality traits in pure conditions of depressive/anxiety disorders and alcohol dependence but also in the comorbid condition of depressive/anxiety disorders and alcohol dependence. This chapter is based on cross-sectional NESDA data and considers various aspects of negative emotionality and impulsivity as the most important personality traits for these disorders.

• Chapter 8 is based on the baseline and two-year follow-up assessments of NESDA. This chapter examines whether depressive/anxiety disorders as well other risk factors independently predict recurrence (i.e., relapse) in persons with remitted alcohol dependence as well as persistence in persons with current alcohol dependence at baseline.
• Chapter 9 describes the impact of comorbid alcohol use disorders as well as other factors on the course of depressive/anxiety disorders. Analyses are based on the baseline and two-year follow-up assessments of NESDA.
• Finally, Chapter 10 summarizes and discusses the main findings of the studies included in this thesis.
REFERENCES


Medicine 1988; 85:466-471.
DAWSON DA, Grant BF. Should symptom frequency be factored into scalar measures of alcohol use disorder severity? Addiction 2010; 105:1568-1579.


HASIN DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of major depressive disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Archives of General Psychiatry 2005; 62:1097-1106.


SAHA TD, Chou SP, Grant BF. Toward an alcohol use disorder continuum using item response theory: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychological Medicine 2006; 36:931-941.


