CHAPTER 10

GENERAL DISCUSSION
Depressive/anxiety disorders and alcohol use disorders frequently co-occur and have severe consequences such as higher levels of disability, more suicidality and poorer treatment outcomes than pure conditions. The aim of the present thesis was to improve our understanding of the comorbidity of depressive/anxiety disorders and alcohol use disorders in order to optimize prevention and treatment strategies for persons suffering from this impairing comorbid condition. First, we assessed the magnitude of the problem by examining the comorbidity patterns of alcohol use disorders in depressed/anxious persons. Then, the performance of the Alcohol Use Disorder Identification Test, a screening instrument for the detection of alcohol use disorders, was tested in depressed/anxious persons versus healthy controls. Next, we examined the etiological pathways that are involved in the development of the comorbid condition of depressive/anxiety disorders and alcohol use disorders. Finally, we determined the effect of comorbidity on the course of alcohol use disorders as well as on depressive/anxiety disorders.

This chapter will summarize the main findings reported in Chapter 2 through Chapter 9 and will discuss these within the context of the current scientific evidence. In addition, methodological issues as well as implications of our findings for clinical practice will be addressed. Lastly, recommendations for future research and an overall conclusion will be presented.

Comorbidity of depressive/anxiety disorders and alcohol use disorders

First, the lifetime prevalence of alcohol use disorders was examined in NESDA participants with and without lifetime depressive/anxiety disorders (see Chapter 2). Although only 5.5% of persons without a depressive/anxiety disorder met criteria for alcohol dependence, prevalence rates were significantly higher in persons with depressive or anxiety disorders (16.5% and 12.4%, respectively) and especially in persons with both depressive and anxiety disorders (20.3%). In contrast, alcohol abuse was not more common in persons with depressive and/or anxiety disorders than among controls (overall prevalence of alcohol abuse: 11.8%). Our results support the findings of previous general population studies reporting on differential associations for alcohol abuse and alcohol dependence (Kessler et al., 1997; Hasin et al., 2007) and therefore emphasize the importance of distinguishing these two conditions. Since alcohol abuse was not related to depressive/anxiety disorders (see Chapter 2) or other psychiatric disorders (e.g., Hasin et al., 2007), this also raises the question whether DSM-IV alcohol abuse should be considered a genuine psychiatric disorder (see the section of ‘DSM-IV alcohol abuse and dependence versus DSM-5 alcohol-use disorder’ in this chapter).

As the NESDA included a large group of persons with depressive/anxiety disorders as well as healthy controls (Penninx et al., 2008), this sample was highly appropriate for examining comorbidity patterns of alcohol use disorders in depressed/anxious persons. However, the design is less suitable for examining the opposite direction of the association (i.e. to determine the prevalence of depressive/anxiety disorders in persons with alcohol use disorders), because persons with severe substance use disorders were initially excluded from the sample. It is therefore essential to complete this overview with the findings of others. Epidemiological studies have
demonstrated that persons with lifetime alcohol dependence had an increased risk of lifetime depressive/anxiety disorders (Kessler et al., 1997; Lynskey, 1998; Hasin et al., 2005), whereas no associations have been found for alcohol abuse (Kessler et al., 1997; Hasin et al., 2005). This combination of findings again stresses the importance of distinguishing alcohol abuse and alcohol dependence and, additionally, illustrates the limited clinical relevance of a DSM-IV diagnosis of alcohol abuse (see also the section of ‘DSM-IV alcohol abuse and dependence versus DSM-5 alcohol-use disorder’ in this chapter).

**Screening for alcohol use disorders**

Although alcohol use disorders, and especially alcohol dependence, are highly prevalent in persons with depressive/anxiety disorders (see Chapter 2), these problems often remain unrecognized in general psychiatric or somatic clinical settings (Cleary et al., 1988; Rydon et al., 1992). Adequate screening for alcohol use disorders may help to identify those depressed/anxious persons suffering from this comorbid condition. Chapter 3 showed that the Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 1992; Saunders et al., 1993), as a time-efficient screening instrument including just ten items, accurately detected a CIDI-based DSM-IV diagnosis of alcohol dependence in depressed/anxious men (area under the curve [AUC]: 0.89) and women (AUC=0.88) of the NESDA study, which is comparable to its performance in healthy controls. The optimal cut-off point was ≥9 for men and ≥6 for women. The performance of the AUDIT was similar for persons treated in primary care versus outpatient mental health care settings and, in addition, was not changed by the severity of depressive or anxiety symptoms. Screening with the AUDIT can therefore help to identify depressed/anxious persons suffering from this comorbid condition and gives clinicians the opportunity to offer more suitable therapy considering the additional alcohol dependence. The accuracy of the AUDIT in identifying alcohol abuse was, however, limited and no adequate cut-off points could be determined.

**Possible pathways to comorbidity**

To optimize prevention and treatment strategies for the comorbidity of depressive/anxiety disorders and alcohol use disorders, it is crucial to unravel the etiological pathways to comorbidity. Therefore, the present thesis prospectively examined whether depressive/anxiety disorders predicted the first-incidence of alcohol use disorders (see Chapter 4) and/or whether alcohol use disorders predicted the first-incidence of depressive disorders (see Chapter 5). To determine whether other factors better explained these associations, it was essential to take into account the effects of risk factors such as sociodemographics and vulnerability factors. As discussed in Chapter 1, it was also important to consider the heterogeneity of disorders as associations may be conditional on the status (remitted versus current disorder), type (specific disorder) and/or severity of disorders. Finally, we explored the role of shared vulnerability factors in explaining the comorbidity of depressive/anxiety disorders and alcohol use disorders.
Depressive/anxiety disorders predicting the onset of alcohol use disorders

Chapter 4 examined the first-incidence of alcohol use disorders during a four-year follow-up in the NESDA sample. We found that the number of current depressive/anxiety disorders at baseline, as a measure for severity, was a strong and significant predictor for the first-incidence of alcohol dependence, but not for alcohol abuse. The association with alcohol dependence remained significant after taking into account the effects of other risk factors such as sociodemographics, vulnerability factors and addiction-related factors. In addition, similar associations were found for men and women as well as groups based on recruitment setting (i.e., general population, primary care and outpatient mental health services). These findings are consistent with a causal model in which depressive/anxiety disorders induce the onset of alcohol dependence. The ‘self-medication hypothesis’ (Quitkin et al., 1972) might be an underlying mechanism for this association as it suggests that depressed or anxious persons misuse alcohol to reduce their distressing symptoms and, consequently, have an increased risk of developing alcohol dependence. This is supported by previous studies showing that 10-20% of depressed/anxious persons reported the use of alcohol in order to improve their mood or reduce their fears (Bolton et al., 2006, 2009). In addition, a recent prospective study demonstrated that self-medication predicted the first-incidence of alcohol dependence in anxious patients (Robinson et al., 2011).

Previous studies on the role of depressive/anxiety disorders in predicting the first-incidence of alcohol dependence have reported inconsistent findings (Kushner et al., 1999; Gilman and Abraham, 2001; Crum and Pratt, 2001; Zimmerman et al., 2003; Marquenie et al., 2007; Merikangas et al., 2008; Buckner and Turner, 2009; Grant et al., 2009; Swendsen et al., 2010; Behrendt et al., 2011). These conflicting results may be explained by the heterogeneity of depressive/anxiety disorders. This is supported by Chapter 4 showing that the association with first-incident alcohol dependence was conditional on the status and severity, but not the type, of depressive/anxiety disorders. As we found that current depressive/anxiety disorders, but not remitted disorders, predicted the first-incidence of alcohol dependence, this may explain some of the previous inconsistencies since studies reporting positive associations were based on current disorders (Marquenie et al., 2007), whereas studies reporting non-significant associations were based on lifetime disorders (Crum and Pratt, 2001; Zimmerman et al., 2003). Some of the reported inconsistencies might also be explained by differences in severity of disorders as we found that the risk of first-incident alcohol dependence increased with the number of current depressive/anxiety disorders or the severity of depressive and anxiety symptoms.

Alcohol use disorders predicting the onset of depressive/anxiety disorders

Although Chapter 4 showed that depressive/anxiety disorders were a risk factor for the onset of an alcohol use disorder, the opposite direction of the association might also be true: alcohol use disorders as predictors of the onset of depressive/anxiety disorders. Previous prospective general population studies have shown that alcohol
dependence, but not alcohol abuse, was a significant predictor of the first-incidence of anxiety disorders (e.g., Grant et al., 2009), but they failed to find an association with first-incident depressive disorders (De Graaf et al., 2002; Grant et al., 2009). However, Chapter 5 demonstrated that alcohol use disorder severity, as a more informative phenotype, significantly predicted first-incident depressive disorders after 3-year follow-up. For these analyses, we used data of the NESARC, a representative sample of the general population in the United States. The association remained significant after taking into account the effects of other important risk factors such as sociodemographics, vulnerability factors, psychiatric comorbidity and subthreshold depressive symptoms.

These findings indicate that severe alcohol use disorders can cause the onset of depressive disorders. This might be explained by the interpersonal and social consequences often observed in alcohol use disorders (Swendsen and Merikangas, 2000). Our findings may indirectly support this as the risk of first-incident depressive disorders increased with alcohol use disorder severity and was, consequently, especially high in persons with a severe alcohol use disorder. Alcohol use disorder criteria involving interpersonal and social consequences (i.e., social or interpersonal problems [abuse], giving up or reducing activities [dependence] and failure to fulfill roles [abuse]) have shown to be the most severe and are therefore more likely to be present in persons meeting many other criteria (Dawson et al., 2010). Although our study has only considered the first-incidence of depressive disorders, previous studies have suggested that the same underlying mechanism, involving alcohol-related interpersonal and social consequences, might explain the onset of anxiety disorders (e.g., Swendsen and Merikangas, 2000). Future studies are needed to determine the exact mechanisms through which alcohol use disorders predict the onset of depressive as well as anxiety disorders.

In addition, alcohol use may pharmaceutically induce the onset of depressive/anxiety disorders (Falk et al., 2008), for example, through chronic activation of physiological stress systems. This may be supported by our finding that heavy alcohol use was associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system at the NESDA baseline assessment (see Chapter 6). Especially dysregulations of the HPA axis have been linked to depressive/anxiety disorders (Vreeburg et al., 2009; Vreeburg et al., 2010) and may therefore contribute to the observed association between alcohol use disorder severity and first-incident depressive disorders (see Chapter 5). As Chapter 6 is based on cross-sectional data, causal inferences about associations between heavy alcohol use and dysregulation of stress systems are precluded and, therefore, prospective studies are necessary to further clarify causality in the pathways to comorbidity.

Shared vulnerability model
The previous sections showed that depressive/anxiety disorders and alcohol use disorders have a bidirectional relationship in which the first promotes the onset of the other (see Chapter 4) and vice versa (see Chapter 5 and Grant et al., 2009). However,
previous studies have suggested that common factors may independently cause the onset of depressive/anxiety disorders as well as alcohol use disorders (Marquenie et al., 2007; Kendler et al., 1993; Prescott et al., 2000). This shared vulnerability model suggests that common genetic as well as environmental factors explain the onset of comorbidity.

Kendler et al. (2011) has recently provided convincing evidence that two, unrelated genetic structures were underlying depressive/anxiety disorders and alcohol dependence. It is therefore unlikely that genetic predispositions explain the comorbidity of depressive/anxiety disorders and alcohol dependence. This was also supported by Chapter 5 showing that a family history of alcohol dependence, as an indication for a genetic vulnerability for alcohol dependence, was not related to the first-incidence of depressive disorders. In addition, a family history of depressive/anxiety disorders, indicating a genetic vulnerability for depressive/anxiety disorders, did not predict the first-incidence of alcohol dependence (see Chapter 4). Chapter 4 further demonstrated that only current depressive/anxiety disorders at baseline, but not remitted disorders, predicted the first-incidence of alcohol dependence, which supports a model in which depressive/anxiety disorders induce the onset of alcohol dependence. A shared vulnerability model in which common risk factors independently cause the onset of depressive/anxiety disorders as well as alcohol dependence is again less likely as one would have expected similar associations for both remitted and current depressive/anxiety disorders.

Although the comorbidity of depressive/anxiety disorders and alcohol dependence may not be explained by common genetic factors, Kendler et al. (2011) found that both conditions share an underlying, environmental factor. Previous studies have suggested that childhood trauma might be an important risk factor that independently predicts the onset of depressive/anxiety disorders as well as alcohol dependence (Swendsen and Merikangas, 2000). This is supported by Chapter 5 showing that childhood trauma is a strong predictor of the first-incidence of depressive disorders, even after taking into account the effects of other risk factors such as alcohol use disorder severity at baseline. However, Chapter 4 demonstrated that childhood trauma was a significant predictor of the first-incidence of alcohol dependence in unadjusted analyses, but did not remain significant after adjustment for severity of depressive/anxiety disorders and other risk factors. Although childhood trauma showed to be an independent risk factor of the first-incidence of depressive disorders (Chapter 5), this combination of findings may suggest that childhood trauma predicts the first-incidence of alcohol dependence but only through a mediating role of depressive/anxiety disorders (Chapter 4).

The same personality traits, as a shared vulnerability mainly resulting from genetics as well as (early) environmental experiences, may also cause the onset of depressive/anxiety disorders as well as alcohol dependence and, therefore, explain their comorbidity. Although previous studies have shown that traits involving negative emotionality were strongly related to depressive/anxiety disorders (e.g., Bienvenu et al., 2001; De Graaf et al., 2002; Spinhoven et al., 2009) and impulsivity to alcohol dependence
(e.g., Clark 2005; Krueger 2005; Acton and Zodda, 2005; Dick et al., 2010), it was, to our knowledge, never tested whether persons with these disorders also shared the same personality traits. Chapter 7 showed that all aspects of negative emotionality and some aspects of impulsivity (disinhibition, boredom susceptibility and hyperactivity/impulsivity) were linked to pure depressive/anxiety disorder, pure alcohol dependence as well as the comorbidity of depressive/anxiety disorder and alcohol dependence, indicating that shared personality traits may cause the onset of both disorders. However, this is only part of the explanation as we also found differences in traits within persons with this comorbid condition, based on the temporal sequencing of disorders. Persons with a primary depressive/anxiety disorder preceding alcohol dependence had higher scores of negative emotionality and lower scores of thrill and adventure seeking (i.e., more typical traits for depressive/anxiety disorders) compared to persons with alcohol dependence preceding depressive/anxiety disorders. This may indicate that these traits predispose persons to develop a depressive/anxiety disorder, which subsequently causes the onset of alcohol dependence. Since these results were based on cross-sectional data, causal inferences about the role of personality in the comorbidity of disorders are precluded. Prospective studies are needed to unravel the exact etiological pathways through which this comorbidity condition emerges (see also the section ‘Future research’ in this chapter).

The role of other risk factors
This thesis showed that depressive/anxiety disorders independently predicted the first-incidence of alcohol dependence, whereas alcohol use disorder severity was an independent predictor of the first-incidence of depressive disorders. Other risk factors, such as sociodemographics and vulnerability factors, also played an important role in the development of a (comorbid) disorder. A complete overview of our findings regarding risk factors of first-incident alcohol dependence and depressive disorders is provided in Chapter 4 and Chapter 5, but in this section we will pay special attention to the role of gender and subthreshold symptoms.

One of the strongest predictors of the onset of psychopathology was gender. For example, Chapter 5 showed that the risk of developing a depressive disorder was doubled in women compared to men, and this association remained significant after adjustment for other important depression risk factors. In contrast, men have a two-fold increased risk of developing alcohol dependence compared to women (see Chapter 4). However, this association could largely be explained by our finding that men had already experienced more severe alcohol problems at baseline than women.

In addition, subthreshold symptoms demonstrated to be strong and independent predictors of the first-incidence of psychopathology. For example, the severity of baseline major depressive disorder symptoms was an independent predictor of the first-incidence of depressive disorders, even after taking into account the effects of other important depression risk factors (Chapter 5). Similarly, the severity of baseline alcohol problems, as based on the total score of the AUDIT (see Chapter 3), was a
strong and independent predictor of first-incident alcohol dependence (Chapter 4). These findings indicate that the development of depressive disorders as well as alcohol dependence are long-term processes involving various stages, which may require specific clinical interventions (see section ‘Clinical implications’).

Comorbidity and the impact on the course of disorders
As Chapter 2 showed that depressive/anxiety disorders and alcohol use disorders frequently co-occur, it is interesting to determine whether this comorbidity affects the course of disorders. Therefore, we used prospective data of the NESDA sample to examine the impact of comorbidity on the two-year course of alcohol dependence (Chapter 8) and depressive/anxiety disorders (Chapter 9).

Chapter 8 demonstrated that severity of depressive and anxiety symptoms predicted the recurrence (i.e., relapse) of alcohol dependence during two-year follow-up in persons with remitted alcohol dependence at baseline, even after taking into account the effects of other risk factors. This indicates that depressive/anxiety symptoms induce the onset of a new episode of alcohol dependence in persons with a history of dependence. The recurrence of alcohol dependence may result from the same underlying mechanism as a first episode (see Chapter 4): persons misuse alcohol to self-medicate their distressing symptoms of depression and anxiety (Quitkin et al., 1972). Although mood plays an important role in the development of a first or recurrent episode of alcohol dependence, depressive and anxiety symptoms did not predict the persistence of alcohol dependence in persons with current alcohol dependence at baseline. This may indicate that current alcohol dependence is a more autonomous condition which involves loss of control over alcohol intake and compulsive drinking (see for example Koob, 1997) and is no longer dependent of mood states.

Chapter 9 focuses on the effects of comorbidity on the persistence of depressive/anxiety disorders. We showed that comorbid alcohol dependence, and especially severe alcohol dependence, predicted the persistence of depressive/anxiety disorders, even after taking into account the effects of other risk factors. It has been suggested that interpersonal and social problems, as specific characteristics of severe alcohol dependence, cause the persistence of depressive/anxiety disorders (Swensen & Merikangas, 2000; see also the section ‘Alcohol use disorders predicting the onset of depressive/anxiety disorders’ in this chapter). This is consistent with our finding that the criteria involving interpersonal and social problems were mainly present in persons with severe alcohol dependence (i.e., giving up or reducing activities [dependence]; 85%; social or interpersonal problems [abuse]: 100% and failure to fulfill roles [abuse]: 60%). However, further research is needed to unravel the exact mechanisms through which severe alcohol dependence leads to an unfavorable course of depressive/anxiety disorders.

DSM-IV alcohol abuse and dependence versus DSM-5 alcohol-use disorder
As discussed in Chapter 1, DSM-IV alcohol dependence has shown to be highly reliable
and valid, whereas questions have been raised about the reliability and validity of a
DSM-IV diagnosis of alcohol abuse (Hasin, 2003; Hasin et al., 2006). These concerns were
confirmed by a study of De Bruijn et al. (2005) showing that most persons with alcohol
abuse were only low level drinkers and showed minimal or no impairments. In addition,
alcohol abuse had a favorable course with a remission rate as high as 81% after one
year (De Bruijn et al., 2006). Moreover, unlike alcohol dependence or all other psychiatric
disorders, alcohol abuse was not associated with other types of psychopathology (e.g.,
Hasin et al., 2007). The present thesis corroborates these findings as we consistently
failed to find associations between depressive/anxiety disorders and alcohol abuse,
whereas strong links were observed for alcohol dependence. For example, Chapter 2
showed that depressive/anxiety disorders were related to alcohol dependence, but
not to alcohol abuse. Depressive/anxiety disorders also predicted the first-incidence
of alcohol dependence, but not of alcohol abuse (see Chapter 4). In addition, alcohol
dependence negatively affected the course of depressive/anxiety disorders, whereas
alcohol abuse did not (see Chapter 9). And finally, Chapter 3 showed that the AUDIT
accurately detected alcohol dependence, but not alcohol abuse. All these findings
call into question whether alcohol abuse should be considered a genuine psychiatric
disorder.

The current version of the DSM (i.e., DSM-IV; American Psychiatric Association,
1994) defines alcohol abuse and alcohol dependence as two distinct and hierarchical
disorders with dependence taking precedence over abuse if criteria for both are met.
However, recent studies have shown that both types of criteria form a single latent
dimension with abuse and dependence criteria interspersed across one underlying
severity spectrum (Kahler and Strong, 2006; Martin et al., 2006; Saha et al., 2006; Keyes et
al., 2010; Shmulewitz et al., 2010). For example, drinking more or longer than was intended
(dependence) and persistent desire or unsuccessful attempts to quit or reduce drinking
(dependence) were the mildest criteria, whereas giving up or reducing occupational,
social and/or recreational activities to drink (dependence) and failure to fulfill major role
obligations (abuse) were the most severe criteria. Recent studies have also suggested
to eliminate the criterion involving alcohol-related legal problems (abuse) because of
its very low prevalence while adding little information to the diagnosis (Dawson et al.,
2010; Keyes et al., 2010), whereas it would be better to include ‘alcohol craving’ as it is a
common clinical symptom (see De Bruijn et al., 2005; Oslin et al., 2009). These findings
have resulted in plans to combine these eleven criteria into one diagnosis of an alcohol-
use disorder in the new version of the DSM (i.e., DSM-5, expected in 2013; see www.
dsm5.org).

The DSM-5 work group has also proposed to distinguish different levels of
severity within the diagnosis of an alcohol-use disorder. This was based on findings of
previous studies showing that the simple count of criteria formed a linear dimension
of alcohol-use disorder severity without any evidence for specific thresholds (Hasin
& Beseler, 2009; Dawson et al., 2010; Dawson & Grant, 2010). The importance of using
severity indicators rather than categorical diagnoses is also highlighted by our findings.
For example, alcohol use disorder severity, as the count of seven dependence and three abuse criteria, significantly predicted first-incidence of depressive disorders (see Chapter 5), whereas DSM-IV diagnoses of alcohol abuse and alcohol dependence in the same sample did not (Grant et al., 2009). In addition, Chapter 9 showed that alcohol dependence was a risk factor for the persistence of depressive/anxiety disorders but that this association was highly conditional on the severity of alcohol dependence. Moreover, severity of alcohol problems was a strong predictor of the recurrence and persistence of alcohol dependence (see Chapter 8). Although the scientific evidence stresses the importance of severity indicators within a DSM-5 diagnosis of an alcohol-use disorder, it will be difficult to make a decision about the diagnostic thresholds as previous studies did not find any evidence for specific boundaries (Hasin & Beseler, 2009; Dawson et al., 2010; Dawson & Grant, 2010). Therefore, future studies are needed to indentify the most adequate cut-off points for the different levels of severity and, in addition, to determine its implications for clinical practice (see also the sections ‘Clinical implications’ and ‘Future studies’).

Methodological considerations
Several methodological issues have already been addressed in the previous chapters. In this section, we will discuss the most important general limitations that need further reflection.

Most studies in this thesis are based on data of the NESDA sample, consisting of adults with a mean age of 42 years at baseline. First-incidence of alcohol dependence, as examined in Chapter 4, should therefore be considered as late-onset alcohol dependence and may differ from alcohol dependence that develops at an earlier stage in life (Li et al., 2004; Hasin et al., 2007). Moreover, risk factors for late-onset alcohol dependence may be different from risk factors for alcohol dependence with an early onset. This may also explain our finding that a positive family history of alcohol dependence was not related to first-incident alcohol dependence in Chapter 4, whereas findings in Chapter 2 and other cross-sectional studies on lifetime alcohol dependence (e.g., Nurnberger et al., 2004) indicated a strong genetic vulnerability for alcohol dependence. Future studies including both younger and older participants are necessary to determine whether etiological pathways for the development of early- versus late-onset alcohol dependence indeed differ.

An important strength of the NESDA study is that we included a heterogeneous sample of persons with DSM-IV depressive and/or anxiety disorders, representing various settings (i.e., community, primary care and outpatient mental health care services) and stages of psychopathology. However, persons with a primary diagnosis of a bipolar disorder, obsessive-compulsive disorder or post-traumatic stress disorder were initially excluded from this study and, consequently, the sample may not be fully representative for all depressed/anxious persons. Reported associations with alcohol dependence (e.g., Chapter 2 and Chapter 4) are likely to be underestimates as previous studies have shown that especially bipolar disorder (e.g., Merikangas et al., 2008) and post-traumatic stress
disorder (e.g., Kessler et al., 1995) are strongly related to alcohol dependence.

In addition, persons with a primary diagnosis of a severe substance use disorder were initially excluded. The NESDA sample was therefore not fully representative for persons with severe alcohol dependence and, consequently, recurrence and persistence rates are likely to be underestimates (Chapter 8). Similarly, it is likely that the comorbidity of alcohol use disorders in persons with depressive/anxiety disorders is higher than reported in Chapter 2. However, the sample may be quite similar to the potential target population for screening with the AUDIT (Chapter 3) as screening is only useful in persons without a known, primary diagnosis of severe alcohol dependence.

Clinical implications

The present thesis provides new insights into the comorbidity of depressive/anxiety disorders and alcohol use disorders. This knowledge can be used to optimize prevention and treatment strategies for persons with this impairing comorbid condition.

Previous studies have shown that alcohol dependence often remains unrecognized in general medical and general psychiatric settings (Cleary et al., 1988; Rydon et al., 1992). Improvements in mental health care should therefore start with better detection of alcohol dependence in order to offer more suitable therapy for depressed/anxious persons also suffering from alcohol dependence. The AUDIT, as an accurate and time-efficient screening instrument, could be used to detect alcohol dependence since its validity was confirmed in a subsample of depressed/anxious persons (see Chapter 3). A next step should be to integrate addiction treatment in general mental health services in order to optimize treatment for depressed/anxious persons with comorbid alcohol dependence. This has the potential to greatly enhance health care as 95% of depressed/anxious persons with severe alcohol dependence still had depressive/anxiety disorder after two-year follow-up (see Chapter 9). Integrated care has also been advocated by others as a means of enhancing communication between care providers, reducing stigma and avoiding artificial separation of various psychiatric problems that otherwise could result in substandard care (Mechanic 1997; Bartels et al., 2004).

In addition, baseline severity of (subthreshold) symptoms appeared to be strong and independent predictors of the onset and course of disorders during follow-up. For example, severity of alcohol problems predicted the first-incidence (Chapter 4) and course (Chapter 8) of alcohol dependence. Similarly, severity of depressive symptoms was a strong and independent predictor of the first-incidence of depressive disorders (Chapter 5) as well as the course of depressive/anxiety disorders (Chapter 9). These findings indicate that the onset and course of psychiatric disorders involve a long-term process with several stages characterized by different levels of severity and, therefore, support the plan in DSM-5 to distinguish levels of severity within diagnoses (see www.dsm5.org as well as the section of ‘DSM-IV alcohol abuse and dependence versus DSM-5 alcohol-use disorder’ in this chapter). This may also implicate that care should be organized through a stepped model in which persons with subthreshold problems start with a low intensity treatment in order to prevent the development of a
full-blown disorder whereas persons with more severe symptoms are offered a higher intensity treatment. Future studies are needed to identify adequate cut-off points for distinguishing different levels of severity that should be targeted by different treatment strategies.

Future research
The present thesis aimed to provide further insight into the comorbidity of depressive/anxiety disorders and alcohol use disorders. Although our research contributed to this important field in psychiatry, more research is needed and, therefore, this section will discuss directions for future research.

- The present thesis showed that depressive/anxiety disorders independently predicted the first-incidence of alcohol dependence, whereas alcohol use disorder severity was an independent predictor of first-incident depressive disorders. Although we have postulated some hypotheses to explain these associations, prospective studies are needed to determine whether these assumptions indeed explain the development of comorbidity. For example, a recent prospective study demonstrated that self-medication predicted the first-incidence of alcohol dependence in anxious patients (Robinson et al., 2011), but much is still unclear about the role of self-medication in depressive disorders. In addition, more research is needed to determine whether social and interpersonal problems, observed in (severe) alcohol use disorders, indeed cause the onset of depressive and anxiety symptoms. Although we found that heavy drinkers showed dysregulations of the HPA axis and autonomic nervous system in a cross-sectional study, prospective studies, and especially neurobiological studies, are necessary to further clarify whether alcohol use pharmaceutically induces the onset of depressive/anxiety disorders.

- We also suggested that shared vulnerability factors may independently cause the onset of depressive/anxiety disorders as well as alcohol dependence and, therefore, explain their comorbidity. Although the twin study by Kendler et al. (2011) showed that two, unrelated genetic structures were underlying these types of disorders while they shared the same environmental factor, more twin studies, such as the Netherlands Twin Register (NTR), are needed to support this finding. In addition, prospective studies are needed to determine whether the same or different personality traits predict depressive/anxiety disorders and alcohol dependence.

- Since the mean age of the baseline NESDA sample was 42 years, first-incidence of alcohol dependence, as discussed in Chapter 4, should best be considered as late-onset alcohol dependence. Future studies including both younger and older participants would provide important additional information by determining whether pathways to the development of early and late-onset alcohol dependence differ. Data from, for example, Tracking Adolescents’ Individual Lives Surveys (TRAILS) would provide a perfect opportunity to examine the onset of psychopathology as this study included adolescents and will follow them through their lives.
GENERAL DISCUSSION

- As persons with bipolar disorder, obsessive-compulsive disorder and post-traumatic stress disorder were initially excluded from NESDA, our sample may not be fully representative for all depressed/anxious persons. Prospective studies including patients with these specific disorders, such as the Netherlands Obsessive-Compulsive Disorder Association study, may be helpful to examine the role of these disorders in the development and course of alcohol dependence.

- This thesis also found that comorbidity of depressive/anxiety disorders and alcohol dependence negatively affected the course of disorders. We, therefore, suggest that mental health care could be improved by integrating treatment strategies for depressive/anxiety disorders and alcohol dependence, which is also advocated by others (Mechanic 1997; Bartels et al., 2004). However, randomized controlled trials are essential to determine whether integrated treatment is indeed more effective than treatment strategies focusing on either depressive/anxiety disorders or alcohol dependence.

- This thesis also indicated that the onset and course of depressive/anxiety disorders as well as alcohol dependence may involve a long-term process with several stages characterized by different levels of severity. We, therefore, support the plan in DSM-5 to distinguish levels of severity within diagnoses. However, more research is needed to identify adequate cut-off points for distinguishing different levels of severity. In addition, future studies are needed to determine whether different treatment strategies are indicated based on the severity of depressive/anxiety disorders and alcohol dependence (or DSM-5 alcohol-use disorder).

In conclusion
Depressive/anxiety disorders and alcohol use disorders have a bidirectional relationship as depressive/anxiety disorders promote the onset of alcohol dependence, whereas alcohol use disorder severity predicts the first-incidence of depressive disorders. In addition, comorbid alcohol dependence negatively affects the course of depressive/anxiety disorders, whereas comorbid depressive/anxiety disorders have a negative impact on the recurrence of alcohol dependence. These findings provide evidence for a vicious cycle in which depressive/anxiety disorders and alcohol dependence are reinforcing each other and emphasize the importance of this comorbid condition for public health. Suggestions for optimizing mental health care include screening for comorbid disorders as well as integrated care for persons suffering from this highly disabling comorbid condition of depressive/anxiety disorders and alcohol dependence.
REFERENCES


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.


KAHLER CW, Strong DR. A Rasch model analysis of DSM-IV alcohol abuse and dependence items in the National Epidemiological Survey on Alcohol and Related Conditions.


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.


