Anxiety disorders in children with autism spectrum disorders: A clinical and health care economic perspective

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Citation for published version (APA):
DISCUSSION

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A Clinical and Health Care Economic Perspective
Outline

In this final part of the dissertation, findings of the previous chapters are integrated and discussed within the light of the four subthemes: Prevalence, Impact, Treatment, and Explorations. For each of these four subthemes, the primary findings are highlighted and further research questions are identified. The discussion also addresses general limitations to the study and ends with some notes about the implications of the findings.

Prevalence

Anxiety disorders are frequently observed in children with ASD with a meta-analytically estimated prevalence rate of approximately 40% (Chapter 1). This prevalence is found to be higher compared to typically developing children (as discussed in Chapter 1) as well as compared to children with ADHD (Chapter 2). The question that follows is why some individuals with ASD develop anxiety disorders, while others do not? In other words: Which factors contribute to the development of anxiety disorders in children with ASD? In our book chapter (Van Steensel, Bögels, Magiati, & Perrin, 2013), we propose a number of factors that may contribute to the development, or maintenance, of anxiety disorders in children with ASD (see Figure 1), which are discussed in more detail below. The factors are presented in a circle to indicate that these factors are not to be seen individually, but that these factors are likely to interact. Research examining these factors is sparse and much more research is needed to empirically support the contribution of these factors, to examine how these factors interact, and eventually to identify which factors can possibly be changed to reduce the risk of – or prevent – anxiety disorders in children with ASD.

First, there are some indications that genes play a role in the development of anxiety disorders in ASD. Similar genetic markers are found for anxiety in children with autism and typically developing children (e.g., Gadow, Roohi, DeVincent, & Hatchwell, 2008). In addition, a study of Lundström et al. (2011) found that a considerable part of the correlation between ASD-trait and anxiety traits, in a sample of twins from the general population, could be accounted for by common genetic effects (of note, this genetic component was found to be larger in children compared to adults). A last (indirect) form of evidence for a possible genetic factor involved in the development of anxiety in ASD comes from studies that point to increased prevalence rates of anxiety disorders, and an increased expression of anxiety traits, among relatives from subjects with ASD (e.g., Murphy et al., 2000).
Second, child characteristics, such as IQ, age, and gender, are likely to contribute to the development of (specific) anxiety disorders. For example, a lower mean age was found to be associated with separation anxiety disorder, while a higher mean age was associated with anxiety in general and generalized anxiety disorder in specific (Chapter 1). Further, a similar developmental pattern in the (symptom) expression of anxiety disorders was found for children with anxiety disorders, with and without ASD (Chapter 3). Meta-analytic results of the prevalence rates of anxiety disorders suggest that a somewhat lower IQ may be a risk factor for anxiety in general and for social anxiety disorder in specific (Chapter 1). Another factor to be considered is gender. This issue has not often been examined in children with ASD (likely due to power issues as ASD is found to be more prevalent in boys). We found indications that gender differences in type and symptom severity of anxiety may be similar for children with anxiety disorders with and without ASD; girls having higher scores for total anxiety symptoms, as well as higher levels of symptoms of social anxiety disorder, specific phobia, and generalized anxiety disorder than boys (Chapter 3).

Third, neuropsychological deficits caused by abnormal brain development in ASD (i.e. ‘ASD-related factors’) may contribute to the development of anxiety disorders in ASD. For example, children with ASD may develop more specific phobias due to ASD-related disabilities such as deficits in motor skills, cognition, orientation, and/or hyper sensitivity (as discussed in Chapter 3). Further, they may be more likely to respond with anxiety to crowded places or unforeseen situations due to deficits in information processing (central coherence). Similar, social skills deficits seen in children with ASD are likely to provoke anxiety in social situations (Bellini, 2006), and having to deal with unpredictable situations involves flexibility, organizing and planning (executive functioning), and may instead result in (more) adherence to routines or rituals (obsessive-compulsive disorder), as a way to cope with such situations. In partial support, a link is found between anxiety and restricted and repetitive behaviors (Spiker, Lin, Van Dyke, & Wood, 2011), social skills deficits (Bellini, 2004), communication deficits (Davis et al., 2011) and sensory over-responsivity (see Green and Ben-Sasson, 2010, for a review).

Fourth, it has been proposed that stress-related factors associated with ASD, which might also be regarded as (specific to ASD) stress (or life-) events, may promote anxiety (Wood & Gadow, 2010). That is, the authors propose that anxiety in ASD is caused by a down-stream consequence of ASD symptoms; ASD symptoms may generate stress (e.g., social confusion, peer rejection, aversive sensory experiences) that lead to negative affectivity in general – or more specifically anxiety – which in turn may lead to increased (social)
avoidance, increased ASD-like behaviors, distress, etc. (Wood & Gadow, 2010). Obviously, other life- or stress events that are not ASD-specific per se, such as physical illness, family break-ups, a loss of a dear friend, change of school/loss of employment may also contribute to the development of anxiety.

Figure 1: Factors associated with anxiety in ASD (Van Steensel, Bögels, Magiati, & Perrin, 2013)

Fifth, family factors are acknowledged to play a role in the development of anxiety disorders in typically developing children (e.g., Bögels & Brechman-Toussaint, 2006), however, these factors are not often proposed for the development of anxiety in ASD. To the author’s best knowledge, there is only one study that examined the relation between ASD symptoms, internalizing problems and family factors in children with ASD (Kelly, Garnett,
Attwood, & Peterson, 2008). This study found that higher family conflict predicted more internalizing problems (and internalizing problems in turn predicted ASD symptoms), and that higher family cohesion predicted fewer internalizing problems (however, this latter relation was no longer significant when family conflict was included in the model). Although findings clearly need to be replicated and a longitudinal design is required to establish temporal precedence, it does suggest that family factors may contribute – to some extent – to internalizing (anxiety) problems found in children with ASD.

Finally, other environmental factors need to be considered. Although these environmental factors have not been investigated for children with ASD specifically, it is likely that environmental factors such as school, community, social support, and the relationships with peers may serve both as a risk factor as well as a protective factor. For example, having contact with peers may well serve as a buffer for anxiety problems (friendship, social support) but can also cause additional stress (how to make/maintain friends, having to interact with peers, etc.) which may lead to anxiety.

Impact

In this dissertation it was found that anxiety disorders are highly similar in children with and without ASD, and that they may follow a similar developmental and gender pattern (Chapter 3). Further, anxiety disorders seem to have a similar impact for children with and without ASD in terms of quality of life (Chapter 3) and costs (Chapter 4). It was noted in this dissertation that when studying childhood disorders, a family perspective should be taken into account in order to estimate societal costs associated with a particular disorder (Chapter 4). That is, having a child with ASD and comorbid anxiety disorders may affect parents’ paid work and daily activities, and these costs were found to consist of 55% of the total non-health care costs (Chapter 4). Thus, not only do ASD and comorbid anxiety disorders affect the child’s daily functioning and quality of life (Chapter 3), it also affects parental paid work and daily activities (Chapter 4). There are also studies reporting that parents of children with ASD have higher levels of stress, and have a lower quality of life compared to parents of typically developing children (e.g., Mugno, Ruta, D’Arrigo, & Mazzone, 2007; Rao & Beidel, 2009; also see Karst & Van Hecke, 2012, for a review). Such findings indicate once more the importance of taking into account a family perspective when studying childhood disorders.
The impact of ASD on both quality of life as well as on costs was larger than the influence of comorbid anxiety disorders; i.e., for quality of life, the influence of ASD severity (measured with the CSBQ) was higher (parameter estimate = -.31) compared to the influence of anxiety (parameter estimate = -.18) (Chapter 3), and ASD-related costs in children with ASD and anxiety disorders were higher (almost €3,500; about 80% of the total costs) compared to costs due to anxiety reasons (almost €600; about 14% of the total costs) (Chapter 4). This is hardly surprising as ASD is a more persistent disorder, affecting multiple domains throughout the lifespan (American Psychiatric Association [APA], 2000). Therefore, quality of life as well as costs may be affected more by ASD than by comorbid anxiety disorders. Nonetheless, anxiety disorders were found to contribute to quality of life over and above ASD-related problems, indicating that when effective treatment options can be established, this may result in an improvement of quality of life. Note that indeed quality of life was improved after anxiety disorders were treated with Cognitive Behavioral Therapy (CBT) (Chapter 5). In addition, costs due to anxiety may be reduced when effective treatment options are available (Chapter 6), however, remaining costs associated with ASD will still be large. That is, of the 142 million euro – the estimated annual societal costs for children with ASD and comorbid anxiety disorders in the Netherlands (Chapter 4) – about 28 million euro (14%) was estimated to be associated with comorbid anxiety disorders, while 114 million euro (80%) was estimated to be associated with ASD.

**Treatment**

Results revealed that CBT is an effective intervention to treat comorbid anxiety disorders and anxiety symptoms in children with ASD, and that CBT for the treatment of anxiety disorders is not differently effective for children with ASD when compared to clinically anxious children (Chapter 5). However, children with ASD may have higher anxiety levels at baseline and therefore they may be less likely to derive at similar end-states. That is, a smaller percentage of children with ASD was found to be free from all anxiety disorders, and they were less likely to fall in the ‘normal range’ for both anxiety levels and internalizing problems after treatment (based on parent reports). Nonetheless, anxiety levels in children with ASD decreased as much as in children with anxiety disorders and several other positive effects were also found; i.e., quality of life improved, ASD-like behaviors decreased, and internalizing-, externalizing-, and other behavioral problems decreased as well (Figure 2).
What remains to be examined is which factors contribute to treatment effectiveness? In other words: Who benefits from anxiety-driven CBT and – perhaps even more important – who does not? Although CBT was highly effective for the treatment of anxiety disorders in children with ASD, it was also found that over a third was not free from their primary anxiety disorder at follow-up. Such findings are also found for CBT in clinically anxious children; e.g., 64% - 72% of clinically anxious children are free from their primary anxiety disorder after treatment (see the review of Cartwright-Hatton, Roberts, Chitsabesan, Fothergill, & Harrington, 2004; and the meta-analysis of In-Albon & Schneider, 2007) meaning that about one third is not. In the literature several factors are found to be associated with a poorer treatment outcome; parental psychopathology, parenting stress, family dysfunction, and child demographic variables (older age, boys) (Silverman, Pina, & Viswesvaran, 2008), although for the latter (child demographic variables) results are rather inconsistent. Whether these factors are similar – or different – for children with ASD remains to be examined. For example, no differences are found between individual and family CBT for the treatment of anxiety disorders in clinically anxious children (e.g., Bodden et al., 2008; Kendall, Hudson, Gosch, Flannery-Schroeder, & Suveg, 2008; and see the meta-analysis of In-Albon & Schneider, 2007), while for children with (moderate symptoms of) ASD, parental involvement is regarded to be beneficial for treatment outcome and the few studies that have examined this issue support this (e.g., Puleo & Kendall, 2011; Sofronoff, Attwood, & Hinton, 2005). Additionally, how many (and who) of the children with ASD remain free of their primary anxiety disorder after one, two or five years, is yet another question that remains to be answered. Studies involving clinically anxious children without ASD suggest that improvement in anxiety is maintained at long term follow-ups (e.g., Barret, Duffy, Dadds, &
Rapee, 2001; In-Albon & Schneider, 2007), however, this may be different for children with ASD (e.g., learned skills may generalize less). Perhaps children with ASD need a few booster sessions after a year or a parent trained as co-therapist, for a better generalization of learned skills over situations and time. However, empirical evidence is needed to support such claims.

While ASD is found to be associated with high (non-) health care costs (Chapter 4), cost-effectiveness studies for psychosocial treatments in children with ASD are quite rare. The study reported about in this dissertation (Chapter 6) was the first to compare CBT for treating anxiety disorders to alternative treatment options in terms of effectiveness and costs. It was found that CBT seems a cost-effective intervention to treat anxiety disorders in children with ASD (Chapter 6). That is, it was found that CBT had a high probability to be more effective than Treatment As Usual (TAU), however, the probability that either intervention was more costly did not differ much. A complication in the interpretation of these findings is that the willingness to pay threshold for a primary anxiety free child with ASD is unknown which prohibits a stronger conclusion. When evaluated against the cost of illness of children with ASD and comorbid anxiety disorders (Chapter 4), it may be worth investing in primary anxiety free children. However, the difference in effect between CBT and TAU regarding QALYs was very small, and the probability that CBT is cost-effective compared to TAU at a willingness to pay of €20,000 per QALY was found to be uncertain. A limitation to this study is that a golden standard alternative to compare CBT with was lacking. That is, CBT was compared to a rather heterogeneous group of interventions, often not specifically targeting anxiety. The sample was too small for subgroup analyses and a more direct comparison to specific TAU interventions would have been preferred. To date, research has not yet established an evidence-based treatment for anxiety disorders in ASD. In fact, the only alternative that has been studied more systematically is the use of medication; more specifically the use of serotonin selective reuptake inhibitors (SSRI’s). Results of these studies however are inconsistent (see Nadeau et al., 2011, for a review). Besides medication, only one study compared CBT directly to an alternative intervention (instead of a comparison to a heterogeneous group of interventions). Sung and colleagues compared CBT to a social-recreational program for the treatment of anxiety in children with ASD. Results demonstrated a decrease in child self-reported anxiety, and no difference in effectiveness was found between the social-recreational program and CBT (Sung et al., 2012). However, replications are needed as well as more research examining other treatment options for anxiety disorders in children with ASD. For example, there is some preliminary evidence that mindfulness training might reduce anxiety problems in anxious children (Burke, 2010; Semple, Lee, Rosa,
& Miller, 2010; Semple, Reid, Miller, 2005), and that this approach is applicable to children with ASD (e.g., Bögels, Hoogstad, Van Dun, De Schutter, & Restifo, 2008; Singh et al., 2011), however, its (cost-) effectiveness for reducing anxiety problems in children with ASD has not yet been investigated.

Explorations

Early ASD symptoms as a risk for later anxiety?

In this dissertation it was found that children with anxiety disorders have more symptoms of ASD in early development (rated retrospectively) compared to typically developing children (Chapter 7). The question that follows is: Are ASD symptoms a risk factor for the development of anxiety disorders, also in the typically developing population? It is proposed that ASD-deficits might be one of the factors that contribute to the development of anxiety disorders in children with ASD (see above). In addition, the study of Hallett, Ronald, Rijsdijk, and Happé (2010) found that ASD-traits in a typically developing sample measured at age 7 contributed to internalizing traits measured at age 12. It might be that ASD-deficits in general – present in milder form in typically developing children, but more severe in children with ASD – leave the child vulnerable to develop anxiety disorders latter in life. These findings might suggest that the underlying etiological model for the development of anxiety disorders may actually be quite similar for typically developing children and children with ASD, however, the ‘weight’ of the factors, and the interaction between factors may be different. That is, it may be that for children with ASD, ASD-deficits contribute more to the development of anxiety disorders, while for typically developing children environmental factors are more important. These tentative suggestions, however, require empirical support from longitudinal studies that focus on more than just one factor. Further, as research has only recently begun to examine anxiety in ASD, more studies are needed to identify etiological risk factors, and to unravel the interesting relation between anxiety and ASD that seems to run both ways; i.e., anxiety disorders are more prevalent in children with ASD (Chapter 1), and ASD symptoms seem more prevalent in children with anxiety disorders (Chapter 7). Note, however, that studies that focus on discriminating anxiety from ASD (symptoms) are also needed since diagnostic ambiguities may explain some part of this relation.
As stated in the introduction, there are multiple ways to assess anxiety (interview, questionnaire, observation, physiological measures) and future research should compare these measures to examine how anxiety can be assessed best in children with ASD. In this dissertation, the psychometric properties of the SCARED-71 (Bodden, Bögels, & Muris, 2009) were investigated for children with ASD (Chapter 8). The SCARED-71 is a questionnaire developed for typically developing children and there is some debate whether or not instruments developed for typically developing children are applicable to children with ASD. In this dissertation, it was found that the SCARED-71 seems a reliable instrument to assess anxiety in ASD; the SCARED-71 demonstrated high internal consistencies, and evidence for construct validity and discriminant validity was found (Chapter 8). However, more research is needed. That is, the screening utility of the SCARED-71 could not be evaluated as all children included in the present study were diagnosed with a comorbid anxiety disorder. Further, it was found that (parental) cutoffs developed for typically developing children might not be representative for children with ASD (Chapter 8).

It was found that children with ASD may be as reliable in reporting about their anxiety as children without ASD (Chapter 8), however, they may report differently about their anxiety (Chapter 3) – and about treatment effectiveness (Chapter 5) – compared to children with anxiety disorders, and compared to typically developing children. That is, children with ASD tend to report fewer, or less severe, anxiety symptoms compared to their parents, while children with and without anxiety disorders tend to report higher anxiety levels compared to their parents (see Figure 3). However, this difference in reporting did not affect the child-parent agreement, which was found similar in children with and without ASD (Chapter 8). Throughout this dissertation, some explanations for the difference in reporting between children with ASD and their parents are given. It was proposed that (1) children with ASD may under-report anxiety symptoms, and/or (2) parents over-report about their child’s anxiety symptoms. With respect to the latter, this might – in part – be due to the overlap between anxiety and ASD symptoms. Alternatively, or additionally, anxiety may be part of the ASD phenotype (e.g., Kamp-Becker, Ghahreman, Smidt, & Remschmidt, 2009) and therefore higher anxiety levels may reflect a true heightened state.
Figure 3. Differences in reporting about the symptoms of child anxiety (SCARED-71) between children and their parents; children with ASD and comorbid anxiety disorders (ASD), children with anxiety disorders (AD), and typically developing children from the general population (controls).

There are several reasons why children with ASD may under-report about their anxiety symptoms. First, children with ASD may have more difficulty to describe their feelings and may be less aware of their inner states. Second, children with ASD may have more trouble filling out questionnaires due to difficulties in perspective taking (e.g., theory of mind difficulties). For example, an item of the SCARED-71 asks about whether the child is afraid of an animal that is not really dangerous. The child said to the administrator that he did not know how to answer this item. The researcher then asked: ‘Well, do you think you are more afraid of animals than other children?’ To which the child responded: ‘How should I know how afraid other children are?’ Third, children with ASD may have different perceptions about certain concepts. For example, a child was asked whether he worried a lot, to which he replied ‘No’. Further questioning revealed that he often thought about whether others would like him, whether he would arrive in time, whether his mom would get ill and die, whether something bad would happen to him, etc. When then replying that his description sounded quite a bit like worrying, he answered; ‘I do not call it worrying, but I cannot stop myself thinking about it’. Fourth, children with ASD may take a global – or general – perspective less into account. An illustration: an email was received from a mother stating that: ‘My son filled in the questionnaire completely on his own, however, I noticed that he answered the questions for the state that he was in at that particular moment. This can be completely different from five minutes ago, or from five minutes later.’ These more qualitative descriptions are interesting and warrant further investigation about the child’s perspective and its’ reporting about his/her anxiety.
Classification of ASD

We explored the possible influence of changing DSM-5 symptom criteria for the classification of ASD (Chapter 9). It was found that about 25% of the children who are currently diagnosed with ASD do not meet symptom criteria for ASD in the DSM-5 (mostly children diagnosed with PDD-NOS, followed by children with Asperger’s syndrome). It was proposed that some of these children might meet criteria for social communication disorder (SCD). However, efforts are needed to clarify in what aspects children with ASD differ from children with SCD. We found that children who meet DSM-5 symptom criteria differed on several aspects from children that did not meet these criteria. We also found that these two groups did not differ with respect to the social domain, which may suggest diagnostic overlap to some extent. However, note that comparing groups on the same measure that was used for classification is somewhat circular and other studies comparing groups on other (ASD) measures that are not used for ASD classification are needed. Further research should also examine which other disorders may share overlap with SCD. For example, in this dissertation it was found that children with anxiety disorders differed from children in the general population with respect to early ASD symptoms (Chapter 7). Most commonly endorsed items were items from the communication domain. In addition, a specific association between early ASD symptoms and latter social anxiety symptoms was found. Social anxiety disorder has an early onset (Bögels et al., 2010; Rapee & Spence, 2004), and research found children with social anxiety disorders to have less facial expressions and a poorer emotion recognition compared to children without anxiety disorders (Rapee & Spence, 2004). It is possible that some features of the clinical phenotype of social anxiety disorder may overlap with SCD, however, research is needed to support this notion.

Figure 4. Possible overlap between social anxiety disorder (SOC), social communication disorder (SCD), and autism spectrum disorder (ASD) in the DSM-5?
To summarize, some overlap in the social domain between children meeting DSM-5 symptom criteria for ASD and children that do not meet DSM-5 criteria (but may possibly have SCD) was found (Chapter 9), and children with (social) anxiety disorders were found to show (moderate) ASD symptoms, most commonly in the communication domain (Chapter 7). These results taken together indicate that there might be overlap between ASD and SCD with respect to the social domain, while some overlap might also exist for social anxiety disorder and ASD (and SCD) with respect to the communication domain (Figure 4). The findings however are very preliminary and must be viewed within the perspective of the study limitations. Clearly, much more research is needed to examine to what extent the clinical phenotype of social anxiety disorder may overlap with – and differ from – SCD, and to what extent the clinical phenotype of SCD differs from ASD.

**Limitations**

General limitations must be addressed and results presented in this dissertation must be interpreted within the light of those limitations. First, the children of the clinical groups (children with anxiety disorders with and without ASD) were all recruited through secondary mental health care centers. Therefore, the sample of children may not be representative for the total population of children with anxiety disorders, with and without ASD. That is, children who are not referred (community samples), who are referred to primary care centers, or who are referred to more specialized (or hospitalized) centers were excluded and therefore results may not be representative for these children.

Second, all children had levels of normal cognitive functioning. This means that findings may not be generalized to children with lower cognitive functioning. There are indications that adolescents with ASD and intellectual disabilities (ID) also have higher anxiety levels compared to adolescents with ID without ASD (e.g., Bradley, Summers, Wood, & Bryson, 2004), and that behavioral treatment (including hierarchy of fears and in vivo exposure, reinforcement, prompting, modeling and in some cases distraction and extinction) might be effective for dealing with anxiety problems in individuals with ID (Jennett & Hagopian, 2008). However, research including individuals with lower IQs is limited and more studies are needed before interferences can be made.

A third limitation is that a comparison group of children with ASD without anxiety disorders is lacking. Such a comparison group would have been preferred to compare societal costs with (Chapter 4), to compare health-related quality of life with (Chapter 3), and to
establish the specificity of the SCARED-71 (Chapter 8). It would also have been beneficial for the exploration of the effects of the DSM-5 criteria (Chapter 9), as now we can only make interferences about a selected sample of children with ASD and comorbid anxiety disorders that is not representative for the total population of children with (high-functioning) ASD.

Fourth, as already mentioned, longitudinal studies are needed to investigate how anxiety and ASD influence each other over time, and to establish factors that may be of relevance in the development of anxiety disorders. All children that participated in this study, however, already had anxiety disorders at baseline (pre-treatment) and therefore we can only establish associations instead of – the more preferred – causal relations between ASD (symptoms) and anxiety.

Finally, long term follow-ups are needed to establish whether treatment effects are maintained over a longer period of time and to investigate which factors predict a positive or negative outcome over time. Cost-effectiveness studies that include a longer time horizon and a more head to head comparison are needed to find out how to treat anxiety disorders in children with ASD best in term of effectiveness and costs. In addition, research should focus on what works for which child as it is possible that some children may benefit more from one treatment whereas other children may profit more from others.

Implications

This dissertation found anxiety disorders to be highly prevalent in children with ASD (Chapter 1). Further, anxiety disorders are more commonly found in children with ASD compared to typically developing children (as discussed in Chapter 1) and children with ADHD (Chapter 2). Considering these findings, it is first of all important that clinicians are aware of the possibility of such comorbidity. Although there is still some debate about whether anxiety disorders must be seen as comorbid disorders or that they must be regarded to be part of the broader autistic phenotype, it seems valid to co-diagnose anxiety disorders in children with ASD. That is, it is found in this dissertation that anxiety disorders may contribute to the daily impairment and quality of life of children with ASD (Chapter 3), that they are associated with additional (societal) costs (Chapter 4), that children with ASD and a particular comorbid anxiety disorder can be differentiated from children with ASD that do not have that particular comorbid anxiety disorder (Chapter 8), and above all that anxiety disorders are treatable conditions (Chapter 5 and 6). It is therefore important to always be alert of – and ideally always screen for – anxiety disorders in children with ASD.
Subsequently, identifying and acknowledging anxiety disorders in children with ASD, may lead to a greater likelihood for those disorders to be treated, and – as was found in this dissertation – treating them may (indirectly) lead to an improvement in quality of life and a reduction in ASD-like behaviors (Chapter 5). Further, it may stimulate research in this area; it may lead to the identification of etiological factors, and to early screening and prevention activities, as well as more (cost-effective) evidence-based treatment options. At present, the use of CBT for the treatment of anxiety disorders in children with ASD is strongly supported by the findings in this dissertation as it was found that CBT is not differently effective for the treatment of anxiety disorders in children with ASD as compared to typically developing children (Chapter 5), and that CBT seems cost-effective compared to TAU (Chapter 6). Although results have to be replicated and more research is needed for the identification of the key CBT components and factors that may reduce or improve the effects of CBT, there is no reason why not use – and implement – CBT for the treatment of anxiety disorders in children with ASD. In addition, not treating anxiety disorders may cause even more impairments in daily activities, a poorer quality of life, more (ASD-like) problems, as well as additional societal costs.