From the DEPARTMENT OF CLINICAL NEUROSCIENCE

Karolinska Institutet, Stockholm, Sweden

INTERNET-BASED

COGNITIVE BEHAVIOUR

THERAPY FOR SOCIAL

ANXIETY DISORDER

-FROM EFFICACY TO EFFECTIVENESS-

Erik Hedman

Stockholm 2011

All previously published papers were reproduced with permission from the publisher.

To Annika

La seule chose qui me manque
ce sont nos doux moments à venir

ABSTRACT

Background: Cognitive behaviour therapy (CBT) is an effective, well-established, but not widely available treatment for social anxiety disorder (SAD). Internet-based cognitive behavior therapy (ICBT) has the potential to increase availability and facilitate dissemination of therapeutic services for SAD. However, research is needed to establish efficacy, effectiveness, long-term effects, cost-effectiveness and potential determinants of treatment outcome.

Aims: The present thesis aimed at investigating the following: a) The efficacy of ICBT for SAD in a university setting (Study I), b) the effectiveness of ICBT for SAD in a psychiatric setting (Study II), c) The effects of ICBT for SAD over 5 years (Study III), d) The cost-effectiveness of ICBT for SAD compared to conventional CBT (Study IV), and e) Clinical and genetic determinants of ICBT for SAD in relation to conventional CBT (Study V).

Methods: Two large scale randomised controlled trials (RCTs) were conducted. In the first RCT (Study I), ICBT (n=40) was compared to CBT bibliotherapy (n=40) and a waiting list control (n=40). The second RCT (Study II) was a non-inferiority trial comparing ICBT (n=64) to cognitive behavioural group therapy (CBGT; n=62) in a clinical setting. In Study III, a 5-year follow-up assessment was conducted of participants of Study I. In Study IV, a prospective cost-effectiveness and cost-utility analysis of ICBT compared to CBGT was conducted using a societal perspective. Based on clinical and genetic data collected in Study II, predictors and moderators of treatment outcome of ICBT in relation to CBGT were investigated in Study V.

Results: Study I: ICBT for SAD yielded large effect sizes on measures of social anxiety and demonstrated superiority to waiting list controls and a trend towards superiority of CBT bibliotherapy. Study II: ICBT for SAD was well within the non-inferiority margin compared to CBGT on the primary outcome measure. Study III: Participants receiving ICBT for SAD made further improvements from post-assessment to 1-year follow-up. These improvements were maintained at 5-year follow-up. Study IV: The incremental cost-effectiveness ratio was -7042 USD, suggesting that ICBT compared to CBGT leads to incremental gains to a lower cost. Study V: Demographic, clinical and therapy related factors predicted outcome of CBT. A few clinical factors moderated treatment outcome of ICBT in relation to CBGT. None of the investigated candidate genes had an impact on treatment outcome.

Conclusions: ICBT for SAD is efficacious, effective in a clinical setting, long-term effective and, compared to conventional CBT, cost-effective regardless of willingness to pay. In addition, treatment outcome can be predicted. ICBT for SAD is ready for implementation and dissemination.

Key Words: Cognitive behaviour therapy, Social anxiety disorder, Internet

ZUSAMMENFASSUNG

Hintergrund: Kognitive Verhaltensterapie (KVT) hat sich in der Behandlung der Sozialen Angststörung (SA) als effektiv erwiesen. Der Zugang zu traditioneller KVT bleibt aber begrenzt. Internetbasierte KVT (IKVT) hat den Vorteil, dass sie vielen Patienten Zugang zu KVT verschaffen kann. Allerdings ist mehr Forschung notwendig, um die kurz- und langfristige Wirksamkeit, sowie die Kosteneffektivität dieser vielsprechenden Therapieform zu evaluieren. Im Weiteren sollten Prädiktoren und Moderatoren des Behandlungserfolgs identifiziert werden.

Ziele: In der vorliegenden Doktorarbeit wurde Folgendes untersucht: a) Die Wirkung einer IKVT zur Behandlung der SA in einem Universitätskontext (Studie I), b) Die Wirkung einer IKVT zur Behandlung der SA in einem klinischen Kontext (Studie II), c) Die langfristige Wirksamkeit der IKVT (Studie III), d) Die Kosteneffektivität der IKVT im Vergleich zu konventioneller KVT (Studie IV), and e) Prädiktoren und Moderatoren des Behandlungserfolgs bei IKVT im Vergleich zu KVT (Studie V).

Methoden: Die Basis für die vorliegende Doktorarbeit bilden zwei große randomisiert-kontrollierte Studien (RCTs). In der ersten Studie wurde eine IKVT (n=40) mit einer Bibliotherapiebedingung (n=40) und einer Wartelistekontrollgruppe (n=40) verglichen. Die zweite Studie wurde als eine non-inferiority-Studie konzipiert, in welcher IKVT (n=64) mit Kognitiv-Behavioraler Gruppentherapie (KBGT; n=62) verglichen wurde. Bei der dritten Studie ging es um eine Langzeit-Katamnese, in welcher Patienten der ersten Studie ein Jahr und fünf Jahre nach Therapieabschluss untersucht wurden. In der vierten Studie wurde die Kosteneffektivität der IKVT im Vergleich zur KBGT untersucht, wobei volkswirktschaftliche Kosten mitberücksichtigt wurden. In der fünften Studie wurden schließlich Prädiktoren und Moderatoren des Behandlungserfolgs bei IKVT im Vergleich zu KBGT exploriert.

Ergebnisse: Studie I: Die IKVT-Bedingung war der Kontrollbedingung statistisch signifikant überlegen, wobei die Effektstärken auf primären Massen der sozialen Angst groß waren. Im Vergleich zur Bibliotherapiebedingung zeigte sich ein Trend zu einer Überlegenheit der IKVT. Studie II: Im Vergleich zu KBGT bewegten sich die Effekte der IKVT auf primären Ergebnismassen im Bereich der definierten Nicht-Unterlegenheitsgrenzen. Studie III: Bei Probanden die mit IKVT behandelt wurden, fanden sich weitere Verbesserungen vom Post- zum 5-Jahres-Katamnese Messzeitpunkt. Studie IV: Im Vergleich zur KBGT erwies sich die IKVT als kosteneffektiver. Die inkrementelle Kosteneffektivitätsrelation betrug -7042 USD. Studie V: Klinische Faktoren sagten den Therapieerfolg in der KVT vorher. Das Ergebnis wurde nicht durch die untersuchten Kandidatengene beeinflusst.

Schlussfolgerungen: Die IKVT zur Behandlung der SA hat sich sowohl in einem experimentellen als auch in einem klinischen Setting als kurz- und langfristig wirksam erwiesen. Unabhängig von der Zahlungsbereitschaft von Kostenträgern, stellt IKVT bei SA im Vergeich zu konventioneller KVT eine kosteneffektive Behandlung dar. Die Implementierung von IKVT zur Behandlung von SA kann empfohlen werden.

Schlüsselwörter: Kognitive Verhaltensterapie, Soziale Angststörung, Internet

LIST OF PUBLICATIONS

I. Furmark T, Carlbring P, Hedman E, Sonnenstein A, Clevberger P, Bohman B, Eriksson A, Hållén A, Frykman M, Holmström A, Sparthan E, Tillfors M, Ihrfelt EN, Spak M, Ekselius L, Andersson G. Guided and unguided self-help for social anxiety disorder: Randomised controlled trial. *Br J Psychiatry* 2009; 195: 440-7.

II. Hedman E, Andersson G, Ljótsson B, Andersson E, Rück C, Mörtberg E, Lindefors N. Internet-based cognitive behavior therapy vs. cognitive behavioral group therapy for social anxiety disorder: A randomized controlled non-inferiority trial. *PLoS ONE* 2011; 6: e18001.

III. Hedman E, Furmark T, Carlbring P, Ljótsson B, Lindefors N, Andersson G. Five-year follow-up of Internet-based cognitive behaviour therapy for social anxiety disorder. *Journal of Medical Internet Research*. Accepted manuscript.

IV. Hedman E, Andersson E, Ljótsson B, Andersson G, Rück C, Lindefors N. Cost-effectiveness and cost-utility of Internet-based cognitive behavior therapy vs. cognitive behavioral group therapy: Results from a Randomized Controlled Trial. *Submitted manuscript.*

V. Hedman E, Andersson E, Ljótsson B, Andersson G, Andersson E, Schalling M, Lindefors N, Rück C. Clinical and genetic outcome determinants of Internet- and group-based cognitive behavior therapy for social anxiety disorder. *Submitted manuscript.*

CONTENTS

LIST OF ABBREVIATIONS

APD	Avoidant personality disorder
ASI	Anxiety Sensitivity Inventory
BAI	Beck Anxiety Inventory
BDNF	Brain derived neurotropic factor
BIB	Bibliotherapy
CBGT	Cognitive behavioural group therapy
CBT	Cognitive behaviour therapy
CI	Confidence interval
COMT	Catechol-O-methyl-transferase
C-Scale	Credibility Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
EQ-5D	EuroQOL-5 dimensions
GSAD	Generalised social anxiety disorder
ICBT	Internet-based cognitive behaviour therapy
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
LOCF	Last observation carried forward
LSAS	Liebowitz Social Anxiety Scale
MADRS-S	Montgomery Åsberg Depression Rating Scale self-report
MINI	Mini International Neuropsychiatric Interview
QALY	Quality adjusted life years
QOLI	Quality of Life Inventory
RCT	Randomised controlled trial
SAD	Social anxiety disorder
SCID-I	Structured Clinical Interview for DSM-IV axis I disorders
SIAS	Social Interaction Scale
SPS	Social Phobia Scale
SPSQ	Social Phobia Screening Questionnaire
SSRI	Selective serotonin reuptake inhibitor
TIC-P	Trimbos and Institute of Medical Technological Assessment Cost Questionnaire for Psychiatry
WLC	Waiting list control
5-HTTLPR	Serotonin transporter protein-linked polymorphic region

1 BACKGROUND

1.1 INTRODUCTION

In his seminal opus on human character and causes of psychic distress from 1621, "The Anatomy of Melancholy", Robert Burton cites the following observation made by Aristotle regarding a patient:

> *"He dare not come into company for he should be misused, disgraced, overshoot himself in gestures and speeches or be sick; he thinks every man observeth him*" [1].

Thus, it seems like the basic psychological features of what today is referred to as social anxiety disorder (SAD) are no new appearances. Of course, the term SAD was unfamiliar to Robert Burton. However, his clinical vignette indicates that what we denote as SAD using contemporary psychiatric terminology has been a psychological phenomenon for centuries.

With the advent of the DSM-III in 1980 [2] SAD, or social phobia, was established as a psychiatric diagnosis adopting the main criteria of persistent fear of social situations based on an exaggerated belief of embarrassment. Although showing a close resemblance to normal shyness, indeed it might be that they are different points on the same continuous scale, SAD is by definition distinctly different in terms of its consequences.

The person affected with SAD has an increased risk of quitting school prematurely [3], being unemployed [4], and developing substance abuse disorders and other psychiatric disorders [5]. Considering that SAD typically has an early onset [6] and often follows a chronic course [7], the suffering accompanying SAD is far from normal. From a societal perspective, the aversive consequences of SAD are costly, which to a large extent is due to the fact that SAD is one of the most common psychiatric disorders affecting up to 15% of the population [8].

In the last 25 years, cognitive behaviour therapy (CBT) has been shown to be effective for SAD and is today the most well-established psychological treatment [9, 10]. However, for several reasons the availability of CBT is limited [11] giving a need for treatments that are as effective as conventional CBT but requiring less resources. Internet-based CBT (ICBT), essentially Internet-delivered bibliotherapy with online therapist contact, seems to meet these criteria [12].

By the time of the drafting of the research plan underlying this thesis, only two randomised trials had been published on ICBT for SAD, both conducted by members of my research group [13, 14]. Although the results were promising several aspects remained to be investigated and I viewed the following as pivotal: a) Can ICBT be efficacious when relying solely on therapist contact via the Internet, b) How effective is ICBT compared to conventional CBT when conducted in a clinical setting, c) Are the effects of ICBT long term enduring, d) Is ICBT cost-effective compared to conventional CBT, and d) Is it possible to identify variables that predict and moderate outcome of ICBT compared to conventional CBT?

The empirical studies, I through V, presented in this thesis are an attempt to answer these questions. In the process of conducting these studies ICBT for SAD has gone from being an interesting experimental treatment with strong potential, to a validated treatment ready for implementation in regular psychiatric care. My hope is that the scientific work presented here has and will contribute to reduced suffering and increased quality of life for the many affected by SAD.

Stockholm, March 2011

1.2 SOCIAL ANXIETY DISORDER (SAD)

1.2.1 Diagnostic features of SAD

As diagnostic characteristics of psychiatric disorders are established through consensus agreements in a constantly ongoing process, what constitutes SAD is by nature unstable over time [15]. There are two internationally adopted systems for classification of psychiatric disorders: the Diagnostic and Statistical Manual of Mental Disorders (DSM) system provided by the American Psychiatric Association [APA; 16], and the International Classification of Diseases (ICD) developed by the World Health Organization [WHO; 17]. The DSM and ICD systems are intended to be non-theoretical and descriptive rather than nosological and based on aetiology [18]. This is essential as it means that, by definition, the SAD diagnosis is nothing more than its symptoms. Thus, once a person previously diagnosed with SAD no longer meets the criteria, he or she no longer has the disorder.

As displayed in Table 1, the latest editions of the two systems, DSM-IV [15] and ICD-10 [19] provide similar but not identical definitions of SAD. In clinical research on psychiatric disorders, the DSM-IV is more widely used than the ICD-10 [20, 21], presumably due to the fact that the DSM-system is devoted entirely to the psychiatric field [15].

SAD first appeared in 1980 in the third edition of DSM (DSM-III). The description was conceptually similar to specific phobias thus assuming a fear limited to few situations yielding minor functional impairment [22]. The diagnostic criteria were revised in the DSM-III-R [23] and the DSM-IV [15] and the name social anxiety disorder was suggested as way of recognising the aversive consequences of SAD [24]. According to the DSM-IV, the main diagnostic feature of SAD is "a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing". More specifically, this could be a fear of sweating or blushing when talking at a job meeting, or a fear of being appraised as inadequate by others when conversing at a party.

A key criterion of the diagnosis is E (DSM-IV), which stipulates that the fear or the accompanying avoidance behaviours yield significant functional impairment. Turk and co-workers provide a good clinical description of this in the report of a SAD patient working as a janitor despite having a college degree and who refuses to accept promotions and pay increase due to a fear of supervising others [25]. This impairment criterion is important as it separates SAD from the occasional social anxiety, which nearly everyone experiences, that can be coped with without profound negative impact.

As can be read from Table 1, the main difference between the DSM-IV and ICD-10 systems is that the latter is somewhat more restrictive. This is shown in that the ICD-10 criteria require a certain number of anxiety symptoms to be reached. In addition, these symptoms must have specific physical aspects, such as blushing or fear of vomiting. This means that individuals whose anxiety is limited to fears of sweating or trembling

in social situation do not fulfil diagnostic criteria according to ICD-10. These differences are likely to explain some of the variance in prevalence rates between studies as described below in the Clinical characteristics section [3].

Table 1. Criteria of social anxiety disorder according to DSM-IV and ICD-10

Criterion	DSM-IV, Description of criterion	ICD-10, Description of criterion
A	A marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing. Note: In children, there must be evidence of the capacity for age-appropriate social relationships with familiar people and the anxiety must occur in peer settings, not just in interactions with adults.	Either (1) or (2): (1) marked fear of being the focus of attention, or fear of behaving in a way that will be embarrassing or humiliating; (2) marked avoidance of being the focus of attention or situations in which there is fear of behaving in an embarrassing or humiliating way. These fears are manifested in social situations, such as eating or speaking in public; encountering known individuals in public; or entering or enduring small group situations, such as parties, meetings and classrooms.
B	Exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic attack. Note: In children, the anxiety may be expressed by crying, tantrums, freezing, or shrinking from social situations with unfamiliar people.	At least two symptoms of anxiety in the feared situation at some time since the onset of the disorder, as defined in criterion B for F40.0 (Agoraphobia) and in addition one of the following symptoms: (1) Blushing, (2) Fear of vomiting, (3) Urgency or fear of micturition or defecation.
C	The person recognises that the fear is excessive or unreasonable. Note: In children, this feature may be absent.	Significant emotional distress due to the symptoms or to the avoidance. Recognition that the symptoms or the avoidance are excessive or unreasonable.
D	The feared social or performance situations are avoided or else are endured with intense anxiety or distress.	Symptoms are restricted to or predominate in the feared situation or when thinking about it.
E	The avoidance, anxious anticipation, or distress in the feared social or performance situation(s) interferes significantly with the person's normal routine, occupational (academic) functioning, or social activities or relationships, or there is marked distress about having the phobia.	Most commonly used exclusion criteria: Criteria A and B are not due to delusions, hallucinations, or other symptoms of disorders such as organic mental disorders (F0), schizophrenia and related disorders (F20-F29), affective disorders (F30-F39), or obsessive compulsive disorder (F42), and are not secondary to cultural beliefs.
F	In individuals under age 18 years, the duration is at least 6 months.	
G	The fear or avoidance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition and is not better accounted for by another mental disorder (e.g., Panic Disorder With or Without Agoraphobia, Separation Anxiety Disorder, Body Dysmorphic Disorder, a Pervasive Developmental Disorder, or Schizoid Personality Disorder).	
H	If a general medical condition or another mental disorder is present, the fear in Criterion A is unrelated to it, e.g., the fear is not of Stuttering, trembling in Parkinson's disease, or exhibiting abnormal eating behaviour in Anorexia Nervosa or Bulimia Nervosa.	
Subtype	Specify if Generalised subtype: the fears include most social situations	

Note: Criteria for ICD-10 refer to the research version.

1.2.1.1 Subtypes of SAD and avoidant personality disorder

One of the major revisions of DSM-III-R was the added possibility of classifying persons with SAD according whether the disorder was generalised (GSAD) or not [23]. The generalised form is characterised by the presence of social anxiety in most social situations rather than just a few, such as a pure public speaking fear, and this classification dimension is retained in the DSM-IV. This change was accompanied by the abolition of the hierarchical relationship between SAD and avoidant personality disorder (APD) present in DSM-III meaning that a diagnosis of SAD could not be present if criteria for APD were met. There is a fairly robust empirical ground for distinguishing between subtypes of SAD, i.e. generalised or not. For example, persons with generalised SAD experience more impairment, have lower rates of spontaneous recovery and are more likely to have a comorbid axis-I disorder [5, 26, 27].

The clinical validity of APD as a distinct category separated from SAD, on the other hand, has been questioned in several studies. Instead, the "continuum hypothesis" has been suggested, meaning that SAD and APD represent the same underlying condition, with APD being a more severe form of SAD [28]. There are several arguments for this. First, the diagnostic criteria of APD are strikingly similar to those of SAD with the main criteria being a persistent pattern of social inhibition, feelings of inadequacy, and hypersensitivity to negative evaluation [29] . Second, APD and SAD tend to coexist. In a review of 13 studies reporting on the comorbidity of SAD and APD, Reich found an average overlap of 52% [30]. Third, persons with SAD with comorbid APD respond to pharmacological [31, 32] and psychological treatments [33, 34], refuting the general criteria of personality disorders as enduring, inflexible and pervasive.

Taken together, findings seem to suggest that a distinction within the social anxiety domain is valid, but that this is to be made between non-generalised SAD on the one hand and GSAD/APD on the other.

1.2.2 Clinical characteristics

1.2.2.1 Feared situations

Several studies have shown that the most commonly feared social situation, among persons with SAD as well as in the general population, is public speaking [8, 35, 36]. Among those with SAD speaking in front of others is feared by as many as 78%-89% [8, 37]. Perhaps due to methodological differences, e.g. how fears are phrased and assessed, there seems to be no distinct order of prevalence of other social fears. In the national comorbidity survey replication (NCS-R), the second and third most common fears were speaking up in a meeting/class (85%) and meeting new people (80%) [35]. In a Swedish study, the second most common fear was being addressed in a group of people (25%) followed by maintaining a conversation with someone unfamiliar (23%) [8].

For most persons with SAD, fearing more than one social situation is the rule. In the NCS-R study, less than one percent of those with life time SAD reported that they feared a single situation. In the same study, 71% feared at least 8 situations which was used as cut-off criterion for generalised SAD.

6

1.2.2.2   Course of illness

SAD is often described as a chronic condition meaning that few of the affected experience spontaneous recovery [e.g. 25, 38]. There are however three central aspects to consider when interpreting studies estimating the course of illness of SAD: a) criteria for remission, b) type of sample i.e. does the cohort comprise a clinical or a community sample, and c) whether SAD has been assessed prospectively or retrospectively.

There is a substantial body of knowledge suggesting that SAD has an early onset. In a large epidemiological study, Kessler and co-workers found that 75% of persons with SAD had an onset earlier than age 15 [6] and other studies have found a mean age of onset between 11 and 13 [6, 39].

Most studies conducted using a retrospective design have found that SAD rarely remits. The duration of SAD reported is typically several decades with duration spans from 19-40 years and remission rates between 27-50% suggesting a chronic course for a majority of the affected [7, 35, 40, 41]. However, when comparing these results to studies using a prospective design the picture is slightly different, meaning that larger proportions remit. In the Early Developmental Stages Study [42] assessing young persons, as many as 89% did not retain their SAD diagnosis at 4-year follow-up, although this rate dropped to 53% if stricter criteria for remission were applied. Compared to prospective studies on clinical samples, these rates of remission are very high. A prospective study examining data from the Harvard/Brown Anxiety Research Program showed that the natural course of SAD in a clinical sample was that 32% of the men and 38% of the women with SAD were in remission at 8-year follow-up.

Taken together, these findings indicate that SAD might indeed be chronic, but this is likely to hold more for persons with SAD seeking treatment than for the general SAD population. A reasonable interpretation of the findings is that the course of SAD might be less stable in children and adolescents, but that when entering adulthood the social anxiety stabilise and spontaneous recovery rarely occurs [43, 44].

1.2.2.3   Functional impairment and sociodemographic correlates

> ”I’m not mentally able to withstand that. I have a social phobia and cannot stand these large crowds of people. But I will certainly write a speech”. – Elfride Jelinek, 2004 Nobel Prize winner in literature on being asked if she would travel to Stockholm to collect the prize in person [45].

There is solid evidence demonstrating that SAD is associated with functional impairment in several life domains [46]. Persons with SAD have an increased risk of unemployment or having a job below ones qualifications [4, 47, 48], have lower academic attainment [8, 40], are more often on disability pension [49] and are functionally impaired by the anxiety in their general social life as well as in close relationships [35]. In addition, SAD leads to reduced quality of life [4, 50], an increased risk of alcohol and drug abuse (see Comorbidity below) [51, 52], and poorer somatic health [49]. Naturally, the causal link between SAD and the impairment domains is difficult to claim on empirical grounds. However, when it comes to the work life domain, persons with SAD attribute their difficulties to social anxiety [4]. In the area of

substance abuse, it has been suggested that the fact that SAD precedes alcohol abuse, and that the effect remains after controlling for relevant potential confounders, makes SAD a unique risk factor [51]. In addition, Ruscio and co-workers found that, when controlling for comorbid psychiatric disorders, SAD remained a significant predictor of severe functional impairment [35].

1.2.2.4   Prevalence

The prevalence rate of SAD has been investigated in more than 40 studies worldwide [36]. Table 2 displays large scale community prevalence studies using samples from the adult general population and DSM-III-R, DSM-IV or ICD-10 criteria. Although it seems clear that SAD is a highly prevalent disorder, the prevalence estimates have been shown to vary considerably across studies.

Several aspects have to been taken into account when evaluating studies on the prevalence of SAD. First, the diagnostic criteria used tend to affect prevalence rates meaning that using DSM-III-R and DSM-IV give higher rates than when using ICD-10 or DSM-III criteria [3, 53]. As pointed out by Furmark, the lifetime prevalence in two similar large scale community studies in the USA, the Epidemiologic Catchment Area Program [53] and the National Comorbidity Survey (NCS) [54] differed from 2.4% (DSM-III criteria) to 13.3% (DSM-III-R criteria).

Second, as the impairment criterion of the SAD diagnosis allows for a significant amount of subjectivity, the demarcation condition separating subsyndromal social anxiety from SAD has an impact on prevalence rate. In a Canadian study, the point prevalence of SAD varied from 18.7% if the impairment criterion was defined as "moderate interference or distress" to 1.9% if the impairment was defined as "marked interference" [55]. Similar effects was observed in a Swedish study where the point prevalence ranged from 15.6% to 1.9% depending on the degree of distress used to define SAD cases [8].

A third aspect to bear in mind when considering prevalence is the length of the observation period. Some studies report the lifetime prevalence, e.g. [53, 56]. This usually means that participants are encouraged to state whether they have fulfilled criteria for SAD during their lifetime. Naturally, this has the effect that prevalence rates increases, in one paper based on the NCS [54], the prevalence dropped from 13.3% to 7.9% when lifetime prevalence was compared to 12-month prevalence.

A very stable finding from epidemiological studies on SAD is that women have a higher risk of developing the disorder [36]. Considering sample size and methodological strengths it is likely that the best estimate is around 1.5:1 [36].

Table 2. Adult prevalence rates of SAD from community-based studies

Study	Prevalence rate	Type of prevalence	Country	N	Year
Slade et al. [57]*	4.7	1-year	Australia	8848	2009
Andrews et al. [58]*	1.3 & 2.3[a]	1-year	Australia	10641	2001
Lampe et al. [47]	1.0 & 1.4[a]	1-month			
Offord et al. [59]	6.7	1-year	Canada	9953	1996
Stein et al. [55]	7.1	Point	Canada	526	1994
Pellisolo et al. [60]	1.9[b] or 7.3[c]	Lifetime	France	13127	2000
	0.9[b] r 2.3[c]	1-month			
Lepine et al. [61]	3.8[a]	Lifetime	France	1787	1995
	2.1[a]	1-year			
Faravelli et al. [37]	3.1	Lifetime	Italy	2355	2000
Furmark et al. [8]	15.6	Point	Sweden	1202	1999
Bijl et al. [62]	7.8	Lifetime	The Netherlands	7076	1998
	4.8	12-month			
	3.7	1-month			
Kessler et al. [6, 63]	12.1	Lifetime	United States	9282	2005
	6.8	12-month			
Magee et al. [3] & Kessler et al. [54]	13.3	Lifetime	United States	8098	1996, 1994
	7.9	1-year			
	4.5	1-month			

Note: *=Used ICD-10 diagnostic criteria (all other studies used DSM-III-R or DSM-IV criteria) [a]=Weighted combined estimate of males and females; [b]=narrow SAD definition, [c]=broad SAD definition

1.2.2.5 Comorbidity

Several epidemiological studies have shown that SAD is associated with an elevated risk of developing other psychiatric disorders [35, 63-65]. In fact, as more than 50% of individuals with SAD have been shown to have another axis-1 disorder in their life time, comorbidity is the rule rather than the exception [35, 65]. The most common comorbid disorders are anxiety disorders (e.g. panic disorder, generalised anxiety disorder) and mood disorders (e.g. major depression) [3, 65, 66]. However, persons with SAD also have an increased risk of developing substance abuse disorders and impulse-control disorders [5, 35, 65]. As mentioned in the Subtypes of SAD section, the comorbidity with avoidant personality disorder has been shown to be as high as 89% [67] in some studies making this diagnosis the most comorbid with SAD, possibly reflecting that both disorders express the same underlying phenomenon.

Prospective studies have shown that SAD typically precedes the comorbid psychiatric disorders, e.g. depression [64] and alcohol dependence [51, 68]. It has also been shown that having SAD typically predicts a more severe form of depression compared to depressed persons without SAD [64]. As stated above, these findings have lead to the suggestion that SAD might be a causal risk factor for developing other psychiatric disorders [52, 64, 68]. However, this hypothesis remains to be corroborated.

1.2.3 Health economic aspects of SAD

The functional impairment associated with SAD [49], together with the epidemiological characteristics of the disorder such as high prevalence [36], early onset [6], and the chronic course [69] contribute to making SAD a costly disorder. The economic consequences are substantial from a societal perspective [70] as well as for the affected individual [71].

Societal costs for SAD can be broadly classified in three different categories [70]. The first is *direct medical costs*, i.e. costs related to health care consumption (e.g. general practioner (GP) visits, pharmacological drugs). The second cost domain is *non-direct medical costs*, which are costs of other health-related services not directly associated with health care (e.g. time spent in self-help groups). Finally, a third important cost domain is *non-medical costs*, which are costs pertaining work and domestic productivity loss [72]. To my knowledge, only one study has been published reporting on the societal costs of SAD in the general population. In that study, conducted in the Netherlands, the total annual per capita cost for SAD was €11 952 (95% CI, 7891-16013) which was significantly higher than the annual costs for persons without psychiatric disorders (€ 2957, 95% CI, 2690-3234) [70]. The costs for SAD remained significantly higher than for controls also after including comorbid disorders as covariates.

In the same study, the annual costs of SAD per million inhabitants ranged from € 574 million (crude estimate) to € 277 million (adjusted for comorbid psychiatric and somatic disorders) [70]. The costs of SAD were largely driven by non-medical costs meaning that costs were a consequence of productivity loss rather than with health care consumption [70]. These data indicate that SAD has a profound societal cost impact and that it is essential to conduct economic evaluations of interventions aimed at treating or preventing SAD.

1.3 AETIOLOGY AND MAINTENANCE OF SAD

As outlined by Ollendick and Hirshfeld-Becker, the developmental process of such a complex psychological phenomenon as SAD, is unlikely to be captured in a few cause and effect relationships that can be easily predicted in a mechanistic model [73]. Nevertheless, this section will start by describing separate factors that might contribute to the development of SAD. This will be followed by a presentation of cognitive behavioural models through which maintenance of SAD can be understood once the disorder is established. Finally, an attempt is made to link these interactive variables together.

1.3.1 Heritability and genetic contribution

Several classical twin studies have been conducted in the area of SAD [74-76]. The estimated genetic contribution of SAD has been shown to vary considerably between studies, yielding a range of explained variance of 25-50% [74, 77, 78]. One unresolved issue in this area is whether there is a specific genetic effect leading to SAD or if genetics give a predisposition to develop internalising psychiatric disorders (e.g. anxiety disorders and major depression) in general. Results from the Missouri Female

Twin Study showed that genetic factors were completely shared between SAD and major depressive disorder indicating a general genetic vulnerability [39]. However, one large study showed that a genetic factor specifically related to SAD was nearly three times stronger than the genetic factor common to internalising disorders, suggesting a more specific predisposition to SAD [75].

Studies assessing the concordance of SAD within twin pairs can yield estimates of the general effect of genetics. However, they say nothing about which specific genes that might be involved. More than 25 studies have shown that allelic variation in the insertion/deletion serotonin transporter gene promoter (5-HTTLPR) polymorphism is associated with characteristics relevant to SAD [79]. The proposed mechanism is that carriers of the Short allele in the Long/Short polymorphism have reduced transcriptional efficiency and that this is associated with less extracellular synaptic serotonin availability yielding elevated amygdala reactivity [80, 81]. Other gene candidates that are less studied but theoretically interesting due to their contribution in amygdala responsivity are the catechol-O-methyltransferase gene (COMTval158met) [82] and brain derived neurotrophic factor (BDNFval66met) gene [80].

Overall, it seems clear that genetic factors play a fairly important role in the aetiology of SAD. Just as clear is that the pathways between genotypic and phenotypic expression are poorly understood and that it is highly likely that the lion's share of the genetic contribution is not to be find in a few polymorphism but in many genes that are perhaps working in complex interactive patterns.

1.3.2 Behavioural inhibition

The temperament trait most studied in relation to SAD is behavioural inhibition which is the disposition to be cautious, quiet, timid, and behaviourally withdrawn when presented to novel stimuli [83, 84]. Symptoms predictive of behavioural inhibition at 21 months of age have been found in infants as young as four months old [85], suggesting an early development of the trait. Prospective studies assessing behavioural inhibition in early childhood (1.3-7.0 years) has demonstrated the trait leads to a 3-4 folded increased risk of SAD at middle childhood [86] and in adolescence [87]. Indicating a close link to SAD in particular, in these studies as well as in retrospective ones [88, 89], the effect of behavioural inhibition was specific to SAD meaning that it was not associated with development of any other anxiety disorders. There seems to be a somewhat stronger link between behavioural inhibition and generalised SAD than to the non-generalised subtype [66, 89], possibly suggesting that generalised SAD might be more contingent on early temperamental dispositions than non-generalised SAD.

1.3.3 Social skills deficit

According to the social skills deficit hypothesis, SAD can at least partially be explained as a result of an inadequate or inappropriate behaviour repertoire leading to negative social encounters [90]. The role of social skills deficit in social skills deficit in social anxiety has been investigated in more than 20 studies [91], however with inconsistent findings. Whereas research on adults has yielded mixed results with several well conducted studies showing no or minimal skills deficit effects [92-94], it is fairly clear

that children with SAD have reduced social skills compared to controls without SAD [91, 95, 96].

Two theoretical difficulties deserve mentioning when discussing aetiological role of social skills deficit in SAD. First, it is of great difficulty to isolate the effect social skills on how one is interpreted by others. In nearly all studies, it is impossible to say if the person with SAD is actually unable to display the adequate behaviour or if he or she performs worse due to debilitating anxiety. Accordingly, some authors have suggested the term performance deficit when referring to the type of behaviours normally investigated in the studies described in this section [97].

Another important aspect of the role of social skills deficits in the development of SAD is whether they constitute a cause or an effect of SAD. Several SAD theorists, such as Rapee & Spence, suggest that it might be both [98]. That is, for some individuals skills deficit may have a direct impact through early aversive social experiences and for others skills deficits could evolve over time due to avoidance behaviours thereby developing into a maintaining factor.

1.3.4 Neurobiological aspects

Located in the limbic system of the brain, the amygdala has been found to play a central role in the neurocircuitry of fear [99]. Using imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), a large number of studies have shown that SAD is associated with hyperreactivity of the amygdala during exposure to social threat stimuli [100-104].
Even more relevant to the understanding of neurobiological processes of SAD and its treatment, one study used a design where participants with SAD were examined using PET before and after treatment with CBT [105]. Participants were randomised to either CBT, citalopram or a waiting list control (WLC). The results showed that the active treatments were superior to WLC and those who received CBT and citalopram had a significantly larger decrease in amygdala reactivity during an anxiogenic public speaking task [105].

On a molecular level, several transmittor systems including the dopaminergic, serotonergic and glutaminergic have been proposed to play a role in the aetiology and treatment of SAD. Using resting state examinations, SAD has been associated with lower striatal dopamine 2 (D2) binding potential compared to healthy controls, suggesting a structural neuroanatomical marker of SAD [106, 107]. As for the serotonergic systems, the accumulated evidence for effect of selective serotonin reuptake inhibitors (SSRIs) for SAD clearly indicates that the serotonergic system is involved in the regulation of social fear [108].

In summary, the limbic system and amygdala in particular seem to constitute a central neurobiological route for expressing, acquiring and extinguishing anxiety in SAD. However, what is being observed in the studies described is the biological footprint of expression of anxiety. Thus, it is not reasonable to claim that for example hyperreactivity of the amygdala aetiologically causes SAD as it could merely be a consequence of other causative factors. Until further prospective data is collected,

neurobiological phenomena could probably best be viewed as mediators of causal factors of SAD.

1.3.5 Cognitive behavioural models

Cognitive behavioural models of psychiatric disorders have their historical roots in behaviour therapy beginning in the early 1960's [109] and can be viewed as an integration of cognitive and behavioural paradigms. In short, the cognitive behavioural model differs from the behavioural in that it not only relies on learning theory but also assumes that behaviour change could be mediated by cognitive processes [110] The reasons for adding cognitive processes to behavioural modals were several, such as a difficulty of accounting for complex human behaviour including language with respondent and operant conditioning [110, 111].

In the following section, I will begin by describing an aetiological view of SAD based on a learning perspective followed by a cognitive perspective. Finally these two perspectives are integrated in the two most validated and disseminated cognitive behavioural models of SAD, developed by Heimberg & Rapee [9] and by Clark & Wells [112].

1.3.5.1   Learning theory

There are two major behavioural principles constituting the core of learning theory, respondent and operant conditioning. Respondent conditioning is the process of associating neutral stimuli with unconditioned stimuli, producing conditioned responses of the previously neutral stimuli similar to those of unconditioned stimuli [113]. The unconditioned stimulus-response pattern refers to basic innate biological processes or reflexes, where the fear response is of undisputed importance to survival.

Figure 1 shows the process of fear acquisition by respondent conditioning. The first documented experiment of fear acquisition in man was conducted in 1920. In that study, Watson and Rayner demonstrated that a 9-month old boy, Albert, could be learned to be afraid of pets by being presented to dogs and rabbits (neutral→conditioned stimuli) while exposed to loud noises (unconditioned stimuli) [114]. As for SAD, the respondent model assumes that social situations have been associated with unconditioned fear stimuli, e.g. humiliation, violence, or exclusion from peers.

Few studies have investigated this hypothesis using SAD samples and the results have been inconclusive. In a clinical sample of patients with SAD, Öst and Hugdahl found that 58% reported a conditioning experience and 13% a vicarious learning experience (indirect conditioning) as a trigger of SAD [115]. More recently, one study found that 56% of persons with non-generalised SAD reported a traumatic social episode prior to SAD onset [116]. This was slightly higher than for the group with generalised SAD (40%), possibly indicating a differential pathway to SAD for the two subgroups. At first glance, a study by Hofmann and co-workers seems to support these findings as 89% of a sample of persons with pure public-speaking SAD stated that they had had experienced direct aversive social conditioning [117]. However, only 15% reported that

SAD was developed at about the same time, and the average time until SAD onset was 21.5 years. In summary, there is some indication that conditioning is involved in the development of SAD. Important to bear in mind is that absence of remembered aversive conditioning experiences not necessarily constitutes a logic falsification of the hypothesis as conditioning is a phenomenon that is independent of conscious processing [118]. Needed are studies with objective assessment of conditioning processes.
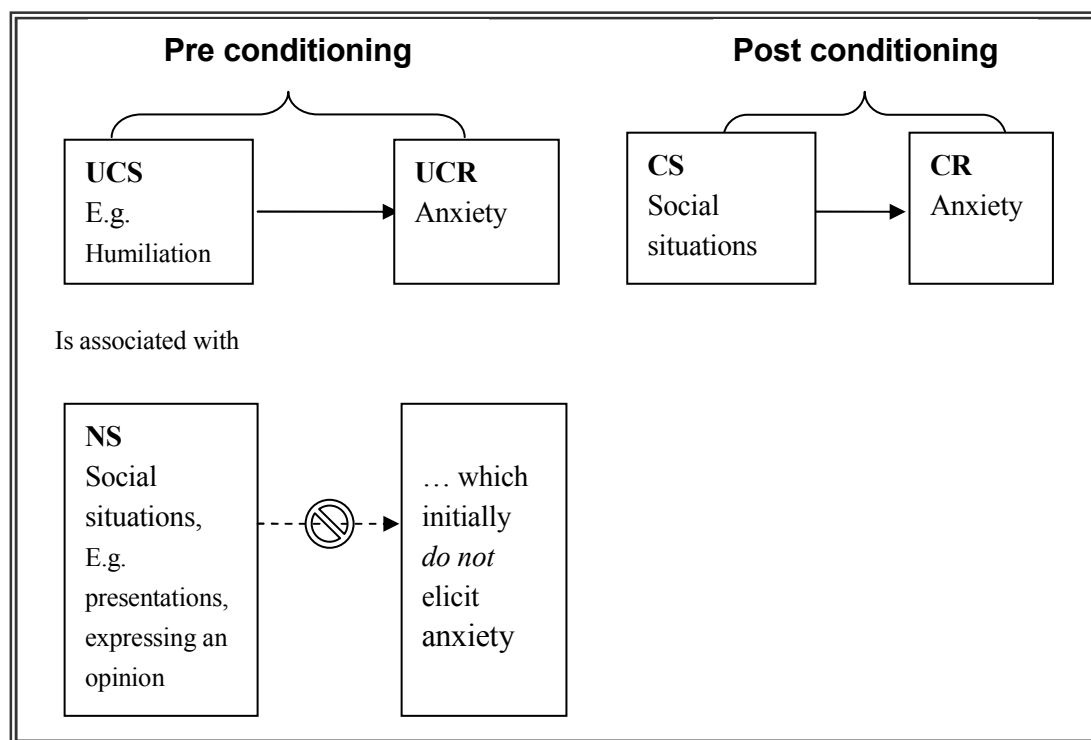
Figure 1. A respondent conditioning paradigm of social anxiety

Abbreviations: UCS, unconditioned stimulus; CS, conditioned stimulus; NS, Neutral stimulus; UCR, unconditioned response; CR, conditioned response

The second major learning principle important for the aetiology of SAD is operant conditioning. Operant conditioning refers to the process of learning through consequences of behaviour [113]. The three basic elements are discriminative stimuli, behaviour and reinforcing/punishing stimuli According to this perspective, central behavioural features of SAD, e.g. avoidance of social situations could have evolved through consequential conditioning by preventing the occurrence of aversive events, i.e. negative reinforcement. Often respondent and operant conditioning are interdependent, i.e., the discriminative stimulus could be a conditioned stimulus eliciting a conditioned response (e.g. anxiety), which is escaped and negatively reinforced through a decrease of the conditioned response, i.e. reduced fear [113]. This type of process is likely to serve a maintaining function of social anxiety as avoidance behaviours prevents, or at least, retards extinction of the conditioned stimulus.

Several studies of early risk factors of SAD indicate the potent effect of avoidance. For example, children with SAD live in families that are less involved in social activities [119] and have parents that are more likely to enhance avoidance through overprotection [120, 121]. Avoidance of social situations, even if it is not maintained

by reduction of conditioned anxiety might be problematic as conditioning of fear is more effective in novel situations. This phenomenon is called latent inhibition [122] and means that having more experience of social situations attenuates the anxiety conditioning if traumatised in a social situation. A final empirical finding indicating the role of avoidance in SAD is the result of a large prospective study which showed that avoidance of social situations predicted maintained SAD at follow-up [123].

1.3.5.2 Cognitive biases in the aetiology of SAD

According to cognitive theory, information processes play a pivotal role in the development and maintenance of SAD [124]. Several cognitive factors have been implied in the aetiology of SAD, such as biased attentional processes, exaggerated belief in the probability and costs of negative social events, as well as distorted memory processing after social events [125]. Regarding attentional processes, studies using dot-probe and modified stroop tests have indicated that persons with SAD have an attentional bias to threat. For example, Asmundson and Stein found that persons with generalised SAD were quicker to respond following cues expressing social threat than to cues signalling physical threat or after neutral stimuli [126]. This pattern was not seen in healthy controls and the results indicate a disorder specific attentional bias.

In the area of estimation of the likelihood of negative events and their costs, one study investigated how persons with SAD interpreted ambiguous social and non-social situations [127]. The results showed that persons with SAD had an increased probability of interpreting social events negatively [127]. Interestingly, this was only the case when picturing oneself in the situation and not when imagining a typical person, suggesting that the bias does not concern a general overestimation of the danger of social events but that is specific to oneself. The tendency to interpret social events negatively has also been reported in studies investigating performance. For example, Rapee and Lim and Voncken and Bögels found that, during public speaking tasks, persons with SAD underestimated their performance compared to control participants [92, 93].

When it comes to biased memory processes, it has been proposed that selective memory of threatening information could play a role in SAD. However, as pointed out by Henrichs and Hofmann, the evidence of a memory bias in clinical samples is limited, perhaps suggesting that information is processed differently depending on the phase of the social interaction [124]. An increased attention in the initial phase followed by avoidant strategies might explain the seemingly illogical finding that attentional biases are poor reflected in memory processes [124]. Importantly, as few studies have been conducted caution in drawing conclusions is warranted.

1.3.5.3 Two integrative cognitive behavioural models of SAD

The cognitive behavioural models proposed by Clark and Wells, and Heimberg and Rapee, respectively, are the most validated and clinically used [112, 128]. As the two models are similar and share many features, this section presents the Clark and Wells' model in detail, followed by a presentation of how the Heimberg and Rapee model differs. An important shared feature of the models is their focus on maintaining factors rather than aetiological factors of SAD.

The Clark and Wells model is based on the idea that persons with SAD develop assumptions about themselves and others (e.g. I'm boring and must be extremely friendly to prevent being rejected) that increases the risk of interpreting social events as threats. Once a situation has been evaluated as dangerous the processes of *self-focused attention*, *in-situation safety behaviours*, *anxiety induced performance deficits* and *pre-and-post event ruminating* contribute to maintaining SAD.

Figure 2 shows the model and the proposed relations between the different parts. When interpreting a situation as socially threatening, a person with SAD directs attentional resources towards himself while perceiving himself as a social object. This has several important consequences. To begin with, interoceptive attention makes it easier to detect anxiety symptoms that otherwise would have gone unnoticed. As these symptoms are themselves often threatening, e.g. blushing, the detection of them increases anxiety in a feed-back loop.
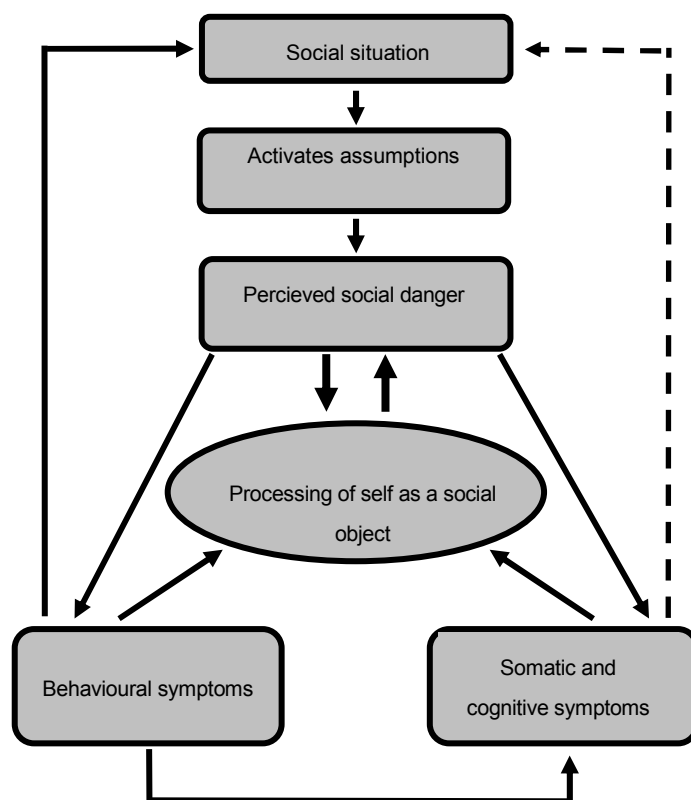
Figure 2. A cognitive behavioural model of social anxiety disorder (Clark & Wells)

In addition, interoceptive attention makes it more difficult to use external information as markers of how one is perceived. Instead, the pounding heart or trembling hands are taken as evidence that one is incapable of handling the situation. To prevent the feared disaster from taking place, the model predicts that the anxious person will use safety behaviours. This could be nearly anything, from wearing multiple layers of clothing to hide sweating from being noticed to drinking alcohol.

These behaviours maintain anxiety for three reasons. First, safety behaviours increase interoceptive attention. Second, it is difficult to attain information that contradicts the

feared event (e.g. not be able to converse without alcohol) from happening. Third, the safety behaviour might actually increase the risk of the feared event (e.g. increased sweating due to more clothes).

Besides safety behaviours and attentional biases, a third component is anxiety induced performance deficits. This means that the anxiety increases the risk of displaying behaviours that could be negatively interpreted by others (e.g. being cold or uninterested) and consequently, the person with SAD might be less friendly treated. This creates negative interaction patterns and confirms negative beliefs. The model also stipulates that persons with SAD are engaged in anticipatory and post-event processing meaning that persons with SAD are anxious long before and after the situation has occurred, selectively remembering past social failures.

In comparison, the model for maintaining SAD proposed by Rapee and Heimberg [128], also stresses the role of the perceived evaluation of others, attention to internal and external threat and representation of oneself as a social object. Furthermore, it also suggests feed-back loops between behavioural, cognitive and somatic anxiety symptoms, attention allocation and risk estimation. The model has a somewhat more detailed description as to how anxiety is the product of a comparison of how the perceived expectations of the audience and one's performance match, taking into account the probability and cost of negative evaluation.

Superficially, some minor differences exist, for example regarding safety behaviours and the role of assumptions. However, on closer examination, the model by Rapee and Heimberg uses the term behavioural symptoms to describe safety behaviours in the same sense as the Clark and Wells model. In addition, the originators state that the model owes much to the thinking behind the Clark and Wells model [128]. The similarity between the models is also acknowledged by Clark and Wells [125].

1.3.6 Concluding remarks on the causes of SAD

As proposed by Rapee and co-workers and by Ollendick and Hirshfeld-Becker, it would be highly unlikely to expect to find a single pathway to SAD based on the risk factors presented above [73, 128]. Instead, it is more probable that many combinations of factors might lead to SAD [73] and that social anxiety is largely a continuous variable where SAD constitutes a certain cutpoint where it becomes clearly debilitating [67, 98].

As suggested by SAD theorists, it is reasonable to assume that a common genetic factor predispose us to developing a cluster of psychiatric disorders, and in combination with at least one other genetic factor, we have a basic degree of social anxiety as a starting point [98]. This level of anxiety can be altered through environmental influences. However, the greater the discrepancy between anxiety endpoint and starting point, the lower the probability. This is because it would require that environmental influences would all have to be in the "right" or "false" direction, which would be unexpected assuming the central limit theorem holds [129].

The pathway to SAD is likely an ongoing interactive process between the person and the surrounding environment [73]. For example, a child might have a behaviourally inhibited temperament that is largely genetically determined [86]. This might increase the probability of having socially anxious parents [130], which in turn could mean less exposure to social situations [119] and thereby poorer possibilities to practice social skills [95]. When starting school, the child is less socially skilled (need not be anxiety driven), which means that he or she is more negatively perceived by other children and is less positively rewarded in social interactions [131]. This in turn, increases avoidance behaviours, which could further increase the distance to other children in terms of capacity to interact with others and perhaps also the risk of being traumatised socially (e.g. bullied) [131]. These aversive experiences are in turn likely to have a more severe effect than on others due to the latent inhibition effect and the aversive conditioned reactions could be maintained by negatively reinforced avoidance or safety behaviours [132].

In order to break this pattern, a potent environmental influence that aims to change the level of social anxiety below the cut point for SAD is cognitive behaviour therapy. In the following section, the content and structure of the therapy is presented. But first, a brief overview of the existing treatment option.

1.4 PHARMACOLOGICAL TREATMENTS

There are two major evidence-based treatments for SAD, pharmacotherapy and CBT. Below, a short presentation of pharmacological treatments for SAD is given followed by a more detailed description of CBT.

Several pharmacological treatments for SAD have been investigated in RCTs, including monoamine oxidase inhibitors (MAOIs) e.g. phenelzine [32, 133], reversible inhibitors of monoamine oxidase A (RIMAs), e.g. moclobemide [134] Selective serotonin reuptake inhibitors (SSRIs), e.g. paroxetine [135], and Benzodiazepines, e.g. atenolol. [32]. Until only about 10 years ago, MAOIs were considered the pharmacological treatment of choice for SAD due to its large effects [136]. However, because of safety issues, e.g. side effects as sleep disturbances and sexual dysfunction, it is today not regarded as the first treatment option [136]. The same reasoning holds for benzodiazepines, i.e. the treatment is effective in treating social anxiety, but could be less safe not at least due to the risk of developing a physical dependence [137].

Instead, during the last 17 years SSRI has emerged as the treatment of choice because of its effectiveness and tolerability. At least 16 placebo controlled double blind trials have been conducted investigating the effect of SSRIs for SAD and in the majority of those the effect sizes have been in the moderate to large range [138, 139]. If discontinuing medication, relapse tends to be the rule rather than the exception, but when adhering to treatment gains are maintained at longer term follow-up [139].

1.5   COGNITIVE BEHAVIOUR THERAPY (CBT)

Aside from CBT, several other psychological treatments have been investigated for SAD, including psychodynamic therapy [140], interpersonal psychotherapy [141] and more recently, attention training [142]. However, to date, CBT is by far the most empirically validated psychological treatment [10]. Reported in a recent review, Ponniah and Hollon identified 37 RCTs documenting the effect of CBT for SAD [143]. Although CBT covers a broad range of interventions, common to nearly all are the components of psychoeducation, exposure to feared social situations, cognitive restructuring and relapse prevention [10, 144]. In the following, I will be focusing on the CBT developed for individual treatment by Clark and Wells [145] as well as the cognitive behavioural group therapy (CBGT) developed by Heimberg and co-workers [22]. This is because they are the best studied and disseminated and because they are of relevance for the treatments delivered in the empirical studies of the present thesis. From this point on, when referring to individual or group CBT, the treatments by Clark and Wells and Heimberg and co-workers, respectively, are implied.

1.5.1   Components of CBT

CBT for SAD is based upon the models presented in the previous section, thus aimed at breaking the vicious cycle between anxiety symptoms, catastrophic interpretations, attention to internal and external threat, safety behaviours and avoidance behaviours. [145]. Common to both individual CBT and CBGT is the formulation of an individual conceptualisation of the patient's problem based on the CBT model. In addition, both treatments put a strong emphasis on weekly home work exercises and entail psychoeducational components, such as describing the nature of anxiety and the rationale for the treatment components. Furthermore, both individual CBT and CBGT include exercises where exposure to social stimuli and cognitive restructuring are integrated, and finally, both entail relapse prevention.

However, in individual CBT, the exposure exercises have a more specific aim of disputing negative thoughts and are typically carried out as behavioural experiments. In contrast, exposure during CBGT is carried out with a slightly more habituation oriented rationale. Whereas CBGT has a very strong emphasis on exposure combined with cognitive restructuring throughout the treatment, individual CBT entails specific interventions aimed at displaying the disadvantages of safety behaviours. This is carried out through experimental like manipulations of safety behaviours while paying close attention to thoughts, anxiety levels and attentional allocation.

In addition, individual CBT includes specific interventions aimed at shifting attention from internal focus to the external situation. In CBGT, external focus is encouraged during exposure, but there are no specific exercises in this area. In summary, individual CBT and CBGT have many vital components in common, but differ in the sense that CBGT has a very profound focus on exposure combined with cognitive restructuring, whereas individual CBT comprises additional interventions specifically related to safety behaviours and attentional shift.

1.5.2 Structure of the treatments

Individual CBT is typically delivered in weekly 1-hour sessions with a single therapist for a duration of 14-16 weeks [145-147]. The treatment starts with creating an idiosyncratic SAD model, followed by manipulation of safety behaviours, exercises in attention shifting, behavioural experiments, strategies for pre and post-event worrying and relapse prevention [145-147]. In CBGT, therapy is lead by two therapists and usually comprises weekly 2.5 hour group sessions for a duration of 12 weeks [22]. Ideally there are 6 patients in the group making a total of 8 persons. Prior to group sessions, there is an individual treatment orientation interview where goals are set and an individual treatment plan is formulated [22]. This is followed by two sessions of psychoeducation and training in cognitive restructuring. After this, sessions 3 through 11 have a strong focus on in-session exposure exercises whereas the final session is devoted primarily to relapse prevention [22].

1.5.3 Effectiveness of CBT for SAD

CBT for SAD has been evaluated in clinical trials for more than 25 years yielding a solid knowledge base. At least four meta-analyses have been conducted specifically devoted to cognitive behaviour therapy [148-151]. In a fairly recent meta-analysis, Fedoroff and Taylor identified 21 trials investigating the effect of treatments entailing exposure and cognitive restructuring. When combining these studies, they found an average within group effect sizes of Cohen's d=0.83 (95% CI, 0.71-0.97) on measures of social anxiety, indicating large effects [150]. However, this pre-post design did not control for confounders, meaning that it is difficult to attribute the effect to CBT. Using a slightly different meta-analytic approach including only studies using control groups, Gould and co-workers found that the between group effect size for the 16 studies investigating CBT was d=0.74 (95% CI, 0.54-0.94) [151] suggesting that CBT has a substantial effect compared to control conditions.

When interpreting this effect size estimate there is one important methodological aspect to bear in mind. The quality of the control conditions vary greatly where waiting-list controls hardly control for much more than the passage of time, whereas some use psychological or pharmacological placebo. Considering this, an interesting finding in a meta-analytic study by Taylor and co-workers was that CBT (exposure plus cognitive restructuring) was superior not only to waiting list controls but also to placebo [149]. Although the empirical support for CBT is strong, important to note is that far from all patients achieve remission. Even in the studies yielding the highest average effect sizes, only 75% of the patients make substantial improvements [146].

Of specific relevance to this thesis, CBGT is the psychological treatment with largest empirical support. It has been investigated in at least 12 RCTs and demonstrated superiority over psychological [9] and pharmacological placebo [133, 152]. Individual CBT employing the Clark & Wells protocol has been investigated in at least 5 RCTs and has proven to be superior to flouxetine, pill placebo [147] and psychiatric treatment as usual [153] An important aspect is that CBGT has been investigated in at least seven RCTs independent of the originators, whereas I have only found one study following the Clark and Wells' protocol not reported by the originators [154] Although CBGT is

the most well-studied intervention, treatments following the Clark and Wells' protocol seem to yield slightly higher effect sizes. The following subsection presents evidence regarding the effect of structure (individual or group) on the outcome.

1.5.3.1 Group CBT vs. Individual CBT

Intuitively, there seem to be many advantages of delivering CBT in a group format, some especially important in the treatment of SAD: the group offers a wide array of exposure possibilities, and observing the discrepancies between others' view of oneself and one's actual performance can be used to weakening the belief that anxiety is a valid proxy for objective assessment of appearance. However, this hypothesis has limited support in the literature.

In a meta-analytic study, all evaluated treatments except social skills training had been conducted both as group and individual treatment. Within each treatment stratum, there was no significant difference between the two delivery formats [150]. Of course, there is always a risk of comparing apples and oranges as the group format most often is not the only difference between individual and group CBT. For optimal assessment of the effect of delivery format, the best design would be a study that compares the same content in different formats. One such a study has been carried out in which participants (n=95) were randomly allocated to either individual, group CBT or a waiting list control where both treatments were identical content wise (Clark and Wells' protocol) [145]. The results showed that participants receiving individual CBT were significantly more improved on the primary social anxiety measure [145]. These findings were replicated in a study by Mörtberg and co-workers using a treatment based on the same protocol [153]. The authors found that individual CBT was superior to group CBT (intensive format) displaying large differences in effect sizes when comparing the two types of CBT [153].

Thus, contrary to what could be expected, it might be that the individual format is superior to delivering treatment in group. Several explanations have been proposed. It might be that the techniques involved in cognitive restructuring are too complex too learn in a group format, or perhaps the group format does not allow for the highly individualised analyses needed for optimal planning and execution of exposure exercises [155]. It could also be that anxiety provoked by the group to some extent prevents effective learning when it comes to complex tasks. As Heimberg's CBGT has not yet been compared in this fashion, and the complexity of CBGT is somewhat lower compared to the Clark and Wells model, it is not directly possible to claim that this holds for CBGT. More studies are needed to clarify the moderating effect of treatment content on format and treatment outcome.

1.5.4 Combination of CBT and pharmacological treatments

With two effective types of treatments for SAD (CBT and pharmacotherapy) yielding large effects for some but not for all, a reasonable suggestion is that a combination of the two might produce additional effects. I know of 3 RCTs employing a design where a combination of pharmacotherapy and CBT (or at least partially based on CBT) has been compared to stand alone treatments for SAD [152, 156, 157]. In two trials where

monotherapy with CBT and SSRI (sertraline and flouxetin, respectively) was compared to a combined treatment, no differences were found between treatments at follow-up [156, 157]

In a recently conducted RCT, participants with SAD were allocated to one of four groups: CBGT, phenelzine sulfate (MAOI), combined CBGT and Phenelzine, or to placebo [152]. The results showed that the combined treatment was superior to both monotherapies as well as to placebo.

Important to keep in mind when considering combination treatments for SAD is that monotherapies in general are developed to be stand alone treatments. Hence, there is no firm theoretical ground to assume strong additive effects. An interesting exception is the advancement in the field of combining the partial N-methyl-d-aspartate receptor (NMDA) agonist d-cycloserine (DCS) with exposure therapy. The suggested mechanism, demonstrated in animal models, is that NMDA-receptor activity of the amygdala to some extent mediates the effect of fear extinction and that DCS alters NMDA functioning [158].

In the field of SAD, Hofmann and co-workers demonstrated in a small RCT (N=27) that participants receiving 50 mg doses of DCS prior to each of four exposure sessions made significantly larger improvements (between groups Cohen's d=0.69-1.42) compared to those receiving exposure plus placebo [159]. These findings were replicated in a subsequent larger scaled RCT using the same design [160]. Thus, future combination treatments for SAD might be more directed towards facilitating extinction learning rather than combining treatments designed to work as monotherapies. Future studies need to address if the additive effects of DCS are maintained when using the full CBT treatment.

1.5.5 Determinants of treatment outcome

As stated above, a substantial proportion (25-50%) of those receiving treatment do not respond sufficiently well to treatment [133, 145, 152]. Under these circumstances, identification of outcome predictors and moderators could facilitate: a) reduced dropout rates and number of treatment failures [161, 162], and b) individually tailored treatments [161, 163]. In RCTs, a predictor is a baseline or posttreatment variable that has a main effect on outcome but no interactive effect with treatment condition. A moderator specifies for whom or under which conditions a treatment works [164]. More specifically, in RCTs a moderator is a prerandomisation characteristic that has an interactive effect with treatment condition on the outcome [161]. Previous research on CBT for anxiety disorders has identified three general categories of predictors: patient demographics including personality traits, clinical characteristics, and therapy process variables [163, 165, 166]. In addition, there is a growing body of evidence supporting the role of genetic factors when predicting outcome of treatment with SSRIs for SAD [81].

In terms of patient demographics, employment and marital status have been found to be predictors of outcome in CBT for depression and GAD, and for the course of untreated anxiety disorders [167-169]. When it comes to clinical characteristics, higher symptom

levels, age of onset, comorbid depression and avoidant personality disorder have been suggested to be predictors of treatment outcome following conventional CBT for SAD [170, 171]. In the category of therapy process predictors, expectancy of treatment outcome and treatment adherence have been shown to predict treatment response [172, 173]. Overall, the predictors above fit well onto the CBT-model for SAD, whose proposed mechanism of change is reduced social anxiety by altered cognitions and a reduction of conditioned fear as a result of repeated exposure [22, 112]. Thus, having more social resources and attending therapy could be associated with greater possibilities to expose to social situations.

The fourth and clearly least studied general category of predictors is genetic factors. Allelic variation in the serotonin transporter gene promoter (5-HTTLPR) has been associated with treatment response of SSRI for SAD [81], panic disorder [174] and depression [175]. There is, to my knowledge, only one published study on the association of gene polymorphisms and CBT [176]. In that study, the 5-HTTLPR polymorphism affecting the expression of the serotonin transporter was associated with outcome of CBT for PTSD.

More recently, a functional polymorphism in the catechol-O-methyltransferase gene (COMTval158met) has been associated with limbic activation during exposure to unpleasant stimuli [82]. COMT is an enzyme that catalyses the degradation of catecholamines neurotransmitters such as dopamine and the effect of the COMTval158met is suggested to be mediated by up to a four-fold variation in enzyme activity [82]. A third candidate polymorphism is the brain derived neurotrophic factor (BDNFval66met) gene. Met-carriers of the BDNFval66met have been shown to have impaired ability in extinguishing conditioned fear responses [177], which suggests that it could play a role in CBT for SAD. No published study has yet investigated the predictive effect of these three gene polymorphisms in the treatment of CBT for SAD.

I have found no studies suggesting stable moderators when comparing different forms of CBT for SAD. As the suggested mechanism of change is the same regardless of whether treatment is delivered face-to-face or, pertinent to this thesis, via the Internet, there are few apparent moderating variables. Although the Internet-based CBT employed in this thesis is simple as it entails no advanced features, it might be that computer skills would moderate the treatment effect. This has not been investigated when pitting Internet-based CBT against conventional CBT, but is important as a warranted question is whether CBT delivered via the Internet is suitable for the average patient or only for those highly skilled in computer use.

When assessing predictors and moderators, an important methodological aspect to consider is which dependent variable one tries to foresee. That is, it might be that predictors have different impact on end state symptom severity as compared to symptom change. Accordingly, in a recent review of predictors on outcome of CBT for SAD, Eskildsen and co-workers found that comorbid depression and avoidant personality disorder predicted end state functioning (more symptoms), but to a much lesser degree, improvement [171]. Although power in that study was limited, it might be that CBT works equally well across initial symptom levels in terms of change, but

that those with high initial anxiety levels tend to have higher levels at posttreatment compared to those with lesser symptom burden.

However, as pointed out by several, change is difficult to assess [178]. For example, using change of raw scores might overestimate the change effect of extreme scorers, whereas percent change scores tend to overestimate the effect of low scorers, e.g. a change from 4 to 2 on the Montgomery-Åsberg Depression Rating Scale constitutes a 50% reduction while a clinically more relevant change from 35 to 19 is a mere 46% reduction [178]. Therefore, the use multiple outcome definitions and the use of regression models with untransformed criterion variable scores and first entrance of preassessment scores has been proposed [171, 179], yielding similar effects as the somewhat less intuitive residual gain score approach [178].

In summary, several demographic, clinical, therapy process related, clinical, and genetic factors have been suggested to affect outcome of CBT for SAD. However, there is yet no evidence of the predictive or moderating effect of these variables when comparing conventional CBT to Internet-based CBT.

1.5.6 Availability of CBT

As CBT is a treatment that has existed for only about 25 years and simultaneously has demonstrated effectiveness for a wide range of psychiatric disorders, the demand of CBT has for a long time been exceeding the supply [180]. Consequently, the availability to CBT is limited for many of those suffering for anxiety disorders such as SAD. Several factors contribute to the lack of availability such as a lack of properly trained therapists and high costs for the patient when buying CBT on the private market. In rural areas in countries with low population density such as the United States, Australia, Canada and Scandinavian countries, long distances might severely restrict availability. In a study by Shapiro and co-workers, the availability of CBT in England and Wales was investigated and the results showed that conventional CBT is available for about 1% of those suffering from anxiety disorders and depression [11]. An important finding was that the geographic inequities were substantial as there were up to 20 times more CBT therapists per 100 000 inhabitants in the 10th population decile (highest availability) compared to the 1st [11].

1.5.7 The need for CBT

As the availability to CBT is limited and pharmacotherapy, especially SSRIs, have been shown to be effective in the treatment of SAD, a reasonable question is whether dissemination of CBT is important. Why not just increase the proportion of patients treated pharmacologically? As a matter of fact, several aspects of CBT make it an advantageous treatment. First, a substantial proportion of patients receiving pharmacotherapy experience adverse side effects such as insomnia, weight gain or altered blood pressure [137, 152]. Second, for some patient groups, pharmacotherapy is counter-indicated because of potential safety issues. Third, CBT seems to produce enduring effects even in the absence of maintenance treatment [10], while relapse is common if discontinuing pharmacological treatments [139]. Finally, CBT might be the treatment of patient preference for persons with SAD. Although I have found no

published studies on SAD samples, articles reporting preferences among patient groups with depression and health anxiety have found preference ratios of 3:1 and 18:1 in favour of psychological treatments compared to pharmacotherapy [181, 182]. In conclusion, several important factors suggest that increasing availability to CBT is a crucial objective for psychiatric health care providers.

1.6   INTERNET-BASED CBT (ICBT) FOR SAD

Although the face-to-face encounter is the typical context for psychological treatments, other ways of delivering therapy has been available for more than 35 years [183]. The most widely used alternative method is probably bibliotherapy. Bibliotherapy can be described as a treatment delivered in form of a self-help text with a clear aim of solving problems relevant to a person's therapeutic needs [184]. By the time of conducting Study I of this thesis in 2005, no study had been published study on bibliotherapy with CBT for SAD. However, since then at least three RCTs have been published demonstrating moderate to large effects of CBT delivered as bibliotherapy for SAD [185-187].

With the advent of personal computers and the Internet a new modality of delivering CBT has been made possible - Internet-based CBT (ICBT). CBT delivered via the Internet has been around for just a little longer than 10 years, but has already been found efficacious for a plethora of psychiatric disorders such as panic disorder, major depression, eating disorders and general anxiety disorder [12]. Very recently, colleagues in my research group and I published the first RCT demonstrating efficacy of ICBT for severe health anxiety [188]. Another interesting venue of ICBT research is in the area of irritable bowel syndrome [189, 190].

When referring to treatments facilitated by computers, important to remember is that there is a wide range of treatments with great variability both in terms of therapist-guidance and technical complexity. The former parameter can vary from no contact at all (e.g., just a CD-ROM programme) to therapy conducted through video conferencing yielding just as much live therapist contact as in conventional CBT [191]. As for technical complexity, some treatments rely on specifically designed hard ware enabling virtual reality exposure exercises [192] whereas others rely heavily on online text [13]. In the studies included in the present thesis, the type of ICBT employed and referred to if not otherwise mentioned, follows a structural model originally developed by Ström and co-workers for the treatment of headache [193].

This type of ICBT can essentially be described as guided online bibliotherapy with therapist contact through an Internet-based messaging system resembling e-mail. Thus, the treatment comprises few advanced technical features, is text-based and therapist contact is restricted to online messages that are not in real-time. Content wise, the treatment follows the Clark and Wells' CBT-model developed for individual therapy presented above [112]. A vital part of the treatment is the gradual access to an online self-help text comprising 15 modules, each covering a specific theme (e.g., exposure or cognitive restructuring) completed with a homework component. Table 3 presents the main theme of each module.

The general idea of the treatment is that the modules should provide the patients with the same knowledge and tools as conventional CBT for SAD. The role of the therapist is mainly to provide feedback regarding home work and to grant access to the treatment modules, thereby often not using more than 5-10 minutes weekly per patient [12]. However, the patient can contact the therapist at any time and expect a reply within 24 hours during weekdays. Throughout the treatment, patients have access to an online discussion forum where they can communicate anonymously with other patients receiving ICBT for SAD.

In addition to these main features, several components integrated in the treatment platform facilitate treatment delivery. These include Internet-based work sheets and automatic generated alerts when the treatment deviates from the expected course. For example, this could be when the patient has not logged in for seven days or takes too long when it comes to sending in homework exercises. Furthermore, symptom assessment can be conducted online as the Internet has been shown to be a valid format of administrating self-report questionnaires [194]. This is important from a safety aspect as it enables a secure form of monitoring of patients' depressive symptoms as algorithms for automatic alerts can be programmed making sure that therapists are aware if patients' scores are indicative of risk for suicidal behaviours.

Table 3. Content of the modules of ICBT for SAD.

Module	Main theme	Number of pages
1	Introduction, information on CBT and SAD	19
2	A CBT-model for SAD	20
3	Cognitive restructuring, part I	30
4	Cognitive restructuring, part II	4
5	Behavioural experiments	24
6	Exposure, part I	24
7	Exposure, part I continued	2
8	Exposure, part I continued	2
9	Safety behaviour manipulation, part I	19
10	Safety behaviour manipulation, part II	2
11	Exposure, part II	17
12	Exposure, part II continued	2
13	Psychoeducation on assertiveness	19
14	Summary and relapse prevention	16
15	Relapse prevention	6
	Total number of pages	**246**

Abbreviations: CBT, cognitive behaviour therapy; SAD, social anxiety disorder

1.6.1 Treatment mechanisms of Internet-based CBT for SAD

So, how it is possible that a treatment delivered via the Internet could work? There are several misconceptions when it comes to the treatment of ICBT, not seldom contributing to a slight degree of skepticism towards the treatment [12]. First of all, ICBT for SAD does not mean that one occasionally visits a public webpage to get general advice on how to handle anxiety. On the contrary, ICBT is delivered in a strictly regulated health care context with thorough diagnostic assessment making sure that one receives a treatment specially adapted for SAD. This means that neither the patient nor the therapist is anonymous and that the therapist has the same amount of treatment responsibility as in regular health care. A second important point is that a good therapeutic alliance can be established online and evidence suggests that the access to a therapist might be crucial to yield strong treatment effects [195, 196]. In fact, a meta-analysis by Spek and co-workers showed that the most effective computer-based treatments for anxiety and depression were those with therapist support [196].

A third vital feature of ICBT for SAD as presented in this thesis is that it is not something that primarily takes place on the Internet. Instead, the major mechanism of effect is reduced social anxiety by demanding behaviour change according to CBT principles. Thus, the Internet is a new modality of delivering CBT, and if patients do not engage in repeated structured exposures to social situations, no improvement is expected.

1.6.2 Advantages of Internet-based CBT for SAD

There are several important positive aspects of Internet-based CBT. As it is independent of distance between therapist and patient, treatment can be facilitated in remote low density populated communities. In addition, as there is no real time contact, therapist and patient can work with the treatment at time points where it is best suited, making the process of treating SAD more efficient for both parties. A specific issue often arising in outpatient clinics is that, even if the patient is willing to put several hours per week into the treatment, it could be difficult to get time off from work. Compared to individual CBT, this is even more problematic when conducting group therapy as it means that patients have to take at half a day off weekly for at least three months. This problem never occurs in Internet-based CBT. From a research perspective, ICBT has several advantages. One major is that the firm structure enables high control over the treatment content that the patient is exposed to, making it an ideal delivery format for comparing different treatments.

Finally, perhaps the most important advantage relevant to clinical practice concerns availability. As the therapist spends only around a fifth of the time per patient compared to conventional CBT, each therapist can treat 4-5 times more patients enabling an increased availability to psychological treatment [12]. In addition, as outlined below in the following section, this feature of SAD makes the treatment potentially very cost-effective.

1.6.3 Cost-effectiveness of Internet-based CBT for SAD

As health care resources are limited, Swedish legislation stipulates that a governing principle in the recommendation of subsidies of health care interventions should be cost-effectiveness [197]. Cost-effectiveness analysis is a tool for estimating the summarised expected benefits, harms and costs of implementing a new treatment into clinical practice [198]. It is a combined measure of the incremental costs and effects of a treatment compared to an alternative, such as another treatment or a waiting list control.

The result of a cost-effectiveness analysis is usually presented as the ratio of the net costs to net health benefits between two alternatives, yielding a so called incremental cost-effectiveness ratio (ICER) [198]. Thus, a treatment producing stronger effects to a lower cost is always considered cost-effective, whereas a treatment can differ in effectiveness and be regarded cost-effective depending on the willingness to pay for a better outcome.

Typically, a cost-effective analysis adopts either a disorder specific outcome, such as no longer having the SAD diagnosis, or the more generic outcome of quality adjusted life years (QALYs). In the latter case, the analysis is called cost-utility analysis where a QALY of 1 is equivalent with one year of full health and score of 0 equivalents death. Thus, four years lived with a quality of life of 0.25 yields a total QALY of 1 [199]. The result of a cost-effectiveness analysis or cost-utility analysis can be interpreted as the price that has to be paid in order to achieve an additional case of remission from SAD or an additional year in full health. A treatment in itself can never be defined as cost-effective, as stated above it is always cost-effective in relation to an alternative and in relation to the willingness to pay for an additional improvement. Depending on health care resources and disease, the latter varies. In industrialised countries, a new treatment that yields an additional QALY for less than €50 000 is typically considered cost-effective [200, 201]

When conducting cost-effective analyses, one can either adopt a health care provider or a societal perspective. In the former case, only direct costs of treatment are considered whereas all costs including productivity loss are included the latter. It has been suggested that the societal perspective is superior as it does not favour any special interest [202]. In addition, as the large economic impact of SAD pertains indirect costs, it is reasonable to adopt a societal perspective [70].

In one study investigating the cost-effectiveness of treatments for SAD it was found that conventional CBT (CBGT) seemed to be the least costly intervention compared to conventional CBT and pharmacotherapy with SSRIs over a two year period [151].

As ICBT requires a limited amount of therapist resources, [12, 203], it has the potential of being a more cost-effective treatment than CBGT. This, in turn, could enable a more optimal health care resource allocation thereby increasing accessibility to CBT and reducing wait times. In a study by Titov and co-workers, ICBT has been estimated to be less costly than CBGT and equally effective in reducing symptoms [204]. However, although pioneering work, Titov and colleagues used estimates partly based on

previously published data from an independent study and differences between treatments were indirectly estimated. In addition, the analysis was based on the cost of the intervention only, not considering other medical and non-medical costs which constitute the major part of the societal economic burden of SAD.

To my knowledge, no study has prospectively investigated the cost-effectiveness of ICBT for SAD compared to conventional CBT from a societal perspective.

1.7 FROM DEVELOPMENT TO CLINICAL IMPLEMENTATION

For more than 20 years, there has been a debate as to whether the results of controlled treatment research can be generalised to regular clinical settings [205]. The terms efficacy and effectiveness have been used to denote different kinds of research approaches where the former refers to research focused on high internal validity and the latter on scientific work yielding high external validity [206]. That is, in order to demonstrate a treatment's efficacy it is necessary to establish control over potential confounding variables. To prove a treatment's effectiveness means demonstrating that it works in circumstances resembling clinical routine practice.

Several aspects of efficacy trials have been proposed to reduce generalizability. These include using exclusion criteria that limit the variability of the sample, random allocation to treatment interventions, and the use of specifically trained therapists and assessors who are motivated by research interests [205]. Ideally, in effectiveness trials there is no trade-off between internal and external validity. This means they should fulfil all criteria for efficacy research while simultaneously showing that a treatment works in real-world conditions [206]. When a treatment has been shown to be efficacious, effective, health economically evaluated and possible to administer on a large scale, it can be viewed as suitable for dissemination [206].

By the time of finishing Study I of the present thesis, there were only two published randomised trials, both conducted at Uppsala University in Sweden, in the field of ICBT for SAD [13, 14]. In the first published study, conducted by Andersson and co-workers, ICBT was combined with two 3-hour exposure sessions in an RCT and the results showed a large effect of the treatment [13]. In a subsequent study following the same model but omitting the exposure sessions, while adding weekly supportive telephone calls, the strong effects were maintained [14].

Thus, when conducting study I of this thesis, ICBT for SAD seemed to be a promising treatment option, but neither efficacy nor effectiveness was established. Several highly important aspects remained to be investigated and I deemed the following to be the most pivotal:

a) Is ICBT for SAD efficacious when administered without additional live exposure sessions or weekly phone calls,
b) Is ICBT for SAD feasible and effective when delivered in a psychiatric setting,
c) Is ICBT for SAD long-term effective,
d) Is ICBT for SAD cost-effective compared to conventional CBT,
e) Is it possible to identify determinants of treatment outcome of ICBT for SAD?

Since then, i.e. in the last five years, there has been vast increase in research in the field of ICBT for SAD. In addition to the work conducted by my research group, Titov and co-workers in Austalia have made highly valuable contributions to the field as have Berger and colleagues in Switzerland. [13, 14, 186, 207-217].

The studies included in this thesis have been part of a research development contributing to the goal of bridging the gap between the experimental setting and clinical practice, thereby taking ICBT from a promising idea to an accessible treatment. Starting in a lab setting and finishing in an Internet Psychiatry Clinic, the studies of this thesis reflect the maturation process of ICBT for SAD. In other words, they have been an important part of the journey from efficacy to effectiveness.

2 AIMS OF THE THESIS

2 AIMS OF THE THESIS

The general aim of the present thesis was to investigate clinically relevant effects of Internet-based cognitive behaviour therapy (ICBT) for social anxiety disorder (SAD). Specific aims, presented under the corresponding study, were the following:

Study I
I. To investigate the efficacy of ICBT compared to bibliotherapy and a waiting list control condition in the treatment of SAD. It was hypothesised that ICBT and bibliotherapy would be superior to a waiting list control condition in reducing social anxiety. In addition, ICBT was expected to be superior to bibliotherapy.

Study II
II. To investigate the effectiveness of ICBT SAD compared to the most well-established psychological treatment for SAD – cognitive behavioural group therapy (CBGT) - when administered in a clinical setting. It was hypothesised that ICBT would be at least as effective as CBGT in reducing social anxiety.

Study III
III. To investigate whether ICBT for SAD is long-term effective. It was hypothesised that treatment gains in terms of reduced social anxiety would be maintained five years after receiving therapy.

Study IV
IV. To investigate the cost-effectiveness of ICBT for SAD compared to CBGT from a societal perspective. It was hypothesised that the treatments would generate significant and equivalent societal cost reductions. In addition, ICBT was expected to be more cost-effective than CBGT due to lower costs of treatment and equivalent treatment effects.

Study V
V. To investigate clinical, demographic, therapy process related and genetic predictors and moderators of ICBT and CBGT. It was expected that variables indicating strong social support, less psychiatric comorbidity, treatment adherence and receiving the preferred type of CBT would predict treatment response. In addition, it was hypothesised that non S-allelic carriers of the serotonin transporter gene promoter (5-HTTLPR) polymorphism, and non-met allelic carriers of the catechol-O-methyltransferase (COMTvalmet158) and the brain derived neurotrophic factor (BDNFval66met) gene polymorphisms would have a superior treatment response.

3 THE EMPIRICAL STUDIES

3.1 STUDY I. EFFICACY OF INTERNET-BASED COGNITIVE BEHAVIOUR THERAPY AND BIBLIOTHERAPY FOR SOCIAL ANXIETY DISORDER: A RANDOMISED CONTROLLED TRIAL

3.1.1 Context and aims

Two previous trials have demonstrated that Internet-based cognitive behaviour therapy (ICBT) might be an efficacious treatment for social anxiety disorder (SAD) [13, 14]. Those studies employed additional therapist support, either through live exposure exercises or through weekly telephone calls. However, to date, ICBT in this online only form has not been validated in a randomised controlled trial (RCT). In addition, an important question is how the treatment works when presented as bibliotherapy (BIB), i.e. as a self-help book without additional therapist guidance. A recent trial showed only limited efficacy of pure self-help [185] for SAD although this form of treatment has been successful for other disorders [218]. The aim of the present study was to investigate the effect of ICBT and bibliotherapy compared to a waiting list control condition (WLC).

3.1.2 Methods

3.1.2.1 Trial design

This was a randomised controlled superiority trial within the context of a parallel group study with randomisation in 1:1:1 ratio.

3.1.2.2 Recruitment and participants

All participants were recruited through self-referral. To be eligible for inclusion, participants had to meet the following main criteria: (a) have a primary diagnosis of SAD although allowing for comorbid psychiatric disorders (b) score <31 on the Montgomery Åsberg Depression Rating Scale self-report [MADRS-S; 219] and <4 on the suicide item of the same scale; (c) not undergo any other psychological treatment during the study period; (d) if on prescribed drugs for anxiety/depression, have a constant dosage for 3 months before treatment onset and unchanged throughout the study; (e) be at least 18 years old. SAD diagnosis was established using the research version of the Structured Clinical Interview for DSM-IV axis-I disorders [SCID-I-RV; 220]. Of the 342 individuals who applied to participate, 120 fulfilled all criteria and were randomised to either ICBT (n=40), BIB (n=40) or WLC (n=40). The sample comprised 81 women (67.5%) and 39 men (32.5%), and the mean age was 36.1 years (SD=10.5).

3.1.2.3 Outcome measures

Four social anxiety questionnaires were used as primary outcome measures: the Liebowitz Social Anxiety Scale self-report version [LSAS-SR; 221], the Social Phobia Scale [SPS; 222], the Social Interaction Anxiety Scale [SIAS; 222], and the Social Phobia Screening Questionnaire [SPSQ; 8]. In addition, three secondary measures were used to measure general anxiety, depression and quality of life, respectively: the Beck Anxiety Inventory [BAI; 223], the MADRS-S and the Quality of Life Inventory

[QOLI; 224]. All instruments were administrated via the Internet at pre-treatment (baseline), post-treatment and one-year follow-up. Participants filled out the LSAS-SR every week in order to monitor weekly treatment gains.

3.1.2.4 Treatments

3.1.2.4.1 Internet-based cognitive behaviour therapy

This consisted of the Internet treatment for SAD as outlined in the introduction of the thesis. Main components were the self-help manual, weekly e-mail feedback from an Internet therapist, and an online discussion forum. The duration of the treatment was nine weeks. Therapists were three licensed psychologists and two clinical psychology students in the final semester of the master's degree programme.

3.1.2.4.2 Bibliotherapy

These participants received the complete self-help manual for social anxiety disorder by mail together with an explanatory letter with instructions to complete one module per week, and to fill out the LSAS-SR form online. The manual was thus the same as the one used for ICBT with only minimal changes to the text regarding homework assignments. Participants had no contact with the study team except for the usual online assessments before, immediately after and one-year after treatment. The duration of the treatment was nine weeks.

3.1.2.4.3 Waiting list control

Participants in this group had no contact with each other or with the study team during their waiting period except for reminders via e-mail or SMS to complete the weekly LSAS-SR assessment. Immediately following the waiting period participants were crossed over to ICBT.

3.1.2.5 Statistical analysis

Differential outcomes were evaluated at post-treatment and follow-up by analysis of covariance (ANCOVA) using pretreatment values as covariates. Within-group t-tests were used to evaluate additional improvement from post-treatment to one-year follow-up. Between group t-tests were used as post-hoc tests. Within and between-group effect sizes were calculated, based on the pooled standard deviation, and expressed as Cohen's *d*. Weekly treatment gains were evaluated using repeated measurement ANOVA. In addition to the analyses on the main trial, data were pooled with those from a subsequent RCT including an ICBT and a bibliotherapy arm and re-analysed [186]. This was done to increase power to detect potential differences between ICBT and bibliotherapy. Analyses were conducted according to the intention-to-treat (ITT) principle using last observation carried forward (LOCF) to replace missing data.

3.1.3 Results

3.1.3.1 Attrition

Of the 120 participants 1 (1%) was lost to post-assessment and 12 (10%) to follow-up.

3.1.3.2 Efficacy of ICBT and bibliotherapy

Time course of improvement of ICBT, BIB and WLC is shown in Figure 3. ANCOVAs for post-treatment change, using baseline values as covariates, revealed significant main effects of the group factor (ICBT/BIB/WLC) on all primary (F=11.63-17.81, df=2,114; $p<0.001$) and secondary (F=5.09-11.41, df=2,114; $p<0.01$) outcome measures, indicating differential improvement over the treatment period. Bonferroni-corrected pairwise comparisons showed that both the ICBT and the BIB groups were significantly more improved in comparison to the WLC group on all social anxiety measures ($p<0.001$) as well as on the BAI ($p\leq0.02$), MADRS ($p\leq0.001$) and QOLI ($p\leq0.03$). The ICBT and BIB groups did not differ significantly on any measure ($p>0.10$). There were no corresponding effects of group, i.e. no differential change, at one-year follow-up (F=0.31-2.57, df=2,111, p=0.73-0.08). All pairwise comparisons also remained insignificant ($p>0.10$) at this time. While the ICBT and BIB groups improved significantly ($p<0.05$) from pre-to post-treatment on all measures, additional improvement from posttest to follow-up was noted only in the former group on primary measures (t=2.58-4.12, df=39, p=0.02-0.001).
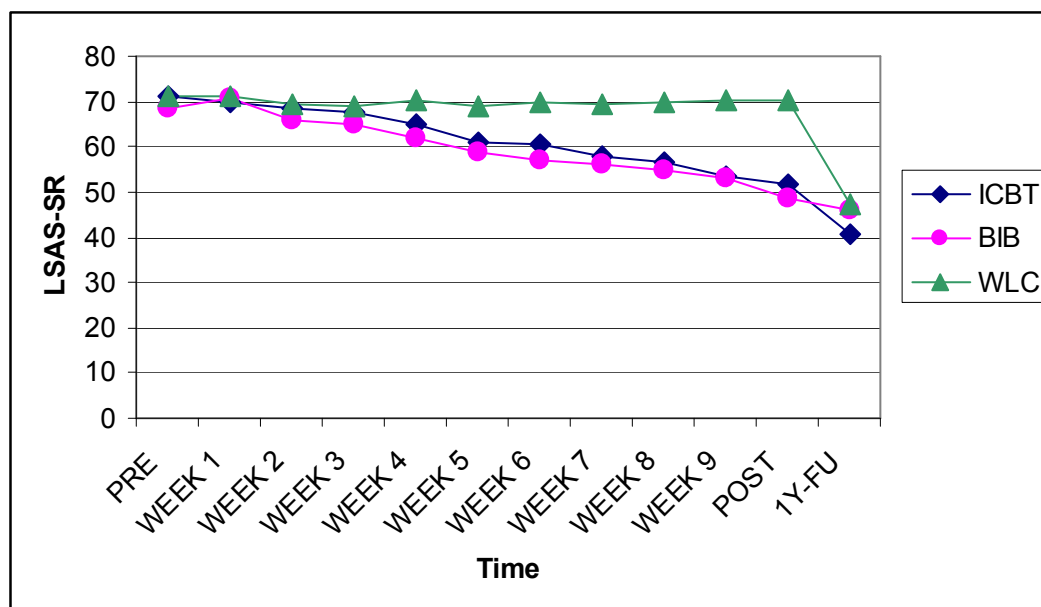
Figure 3. Time course of improvement on the LSAS-SR

Abbreviations: ICBT, Internet-based cognitive behaviour therapy; BIB, Bibliotherapy; WLC, Waiting list control; LSAS-SR, Liebowitz Social Anxiety Scale-self-report; IY-FU, One-year follow-up

3.1.3.3 Effect sizes

For social anxiety measures, effect sizes in the ICBT group ranged between 0.85-1.29 at post-treatment and between 1.10-1.71 at follow-up relative to baseline. The corresponding effect size ranges in the BIB group were 0.67-0.89 and 0.72-1.02. Both ICBT and BIB were associated with moderate to large effect sizes for changes in the BAI and the MADRS-S whereas small to moderate effects were noted for changes in QOLI-scores. The pre-post effect size range on measures of social anxiety in the WLC group was -0.01-0.05.

36

3.1.3.4 ICBT vs. bibliotherapy: Pooled analyses

As stated in the methods section, additional analyses were performed pooling data from the present trial with data from a subsequent trial adopting largely the same ICBT and bibliotherapy in order to increase sample sizes (to n = 69/68), and thus the statistical power. In ANCOVAs for post-treatment change on primary measures, relative to baseline, the group factor (ICBT/BIB) remained insignificant (F=0.10-0.55, df=1, 134, p=0.92-0.44) indicating similar levels of short-term improvement with the two types of treatment.

The corresponding analyses of change between baseline and one-year follow-up revealed a significant effect of group on the SPS (F=4.14, df=1,134, p<0.05) and marginal effects on the SIAS (F=3.54, df=1,134, p=0.062) and LSAS-SR (F=3.89, df=1,134, p=0.051). The adjusted means of these measures indicated better long-term improvement in the pooled ICBT group. While both treatments were associated with significant improvement from pre-to post-treatment, only the pooled ICBT group improved significantly from post-assessment to one-year follow-up. This was noted for primary measures only (t=2.52-4.20, df=68, p=0.014-0.001). The average within-group effect sizes for change on social anxiety measures from baseline to one-year follow-up were 1.33 (pooled ICBT) and 0.89 (pooled BIB).

3.1.4 Discussion

Although the ICBT relied solely on online therapist contact, the treatment proved to be efficacious and yielded equivalent effect sizes on measures of social anxiety compared to previous RCTs that employed some form of additional guidance [13, 14]. Intriguingly, bibliotherapy had significant and reliable effects in persons suffering from SAD. Contrary to expectation, the magnitude of improvement did not differ significantly between ICBT and bibliotherapy immediately following therapy even when pooled data were used. However, only the ICBT group displayed further improvement from post-treatment to follow-up, and a significant difference in favour of ICBT was noted on the SPS a year after treatment.

The present study suggests that neither the Internet-format nor therapist feedback is necessary for obtaining clinical improvement. However, as far from all participants achieved remission, the tendency of ICBT to be superior in the long term should be taken seriously. A limitation of the study is the lack of clinician assessments which meant that all estimates of treatment efficacy relied on self-report.

3.2 STUDY II. INTERNET-BASED COGNITIVE BEHAVIOUR THERAPY VS. COGNITIVE BEHAVIOURAL GROUP THERAPY FOR SOCIAL ANXIETY DISORDER: A RANDOMISED CONTROLLED NON-INFERIORITY TRIAL

3.2.1 Context and aims

Although ICBT for SAD has demonstrated effects in line with cognitive behavioural group therapy (CBGT), which is the most validated and established treatment [9, 10, 38, 143], the current evidence holds a number of limitations [13, 14, 186, 209, 211, 216]. There has been no comparison to conventional CBT, such as CBGT, and most studies have relied solely on self-report instruments as measures of treatment outcome. In addition, most studies have been conducted in university settings, which might have a different impact on treatment experience and outcome compared to receiving care at a psychiatric clinic. Finally, diagnostic procedures may be more clinically valid when conducted in a clinical setting.

In summary, more empirical evidence is needed before ICBT can be validly employed in a psychiatric context. As CBGT is an effective gold standard treatment appropriate for use as a benchmark, the necessary evidence to validate ICBT is to demonstrate non-inferiority (i.e., at least equal effectiveness) to CBGT [225]. The aim of the present study was to compare the effects of ICBT and CBGT for patients with SAD when administered in a psychiatric setting. We hypothesised that ICBT would be at least as effective as CBGT in reducing social anxiety. We also predicted that the two treatments would be equal on secondary outcome measures of depressive symptoms, general anxiety, quality of life, and global functioning.

3.2.2 Methods

3.2.2.1 Trial design

This was a non-inferiority trial within the context of a parallel group study with unrestricted randomisation in 1:1 ratio. The trial was conducted at a psychiatric outpatient clinic and outcome assessors were blind to treatment status.

3.2.2.2 Recruitment and selection

Participants were recruited to the clinic by referral from primary care physicians and psychiatrists, and by self-referral. The main inclusion criteria were largely the same as in Study I. Potential participants were invited to attend an interview with a psychiatrist to confirm the SAD diagnosis and to establish whether they met the remaining inclusion criteria. Of the 230 applicants, 126 met all inclusion criteria and were randomised to ICBT (n=64) or CBGT (n=62). Of the included, 45 (36%) were women and the mean age was 35.4 years (SD=11.4)

3.2.2.3 Outcome measures and assessments

The primary outcome measure was the clinician administered Liebowitz Social Anxiety Scale [LSAS; 226]. The other continuous outcome measures were the same as in Study

I, except that the SPSQ was dropped and that the Anxiety Sensitivity Index [ASI; 227] was added. Axis-I-disorders were established using the SCID-I-RV and the Mini International Neuropsychiatric Interview [MINI; 228]. A treatment credibility scale comprising five items was administered to determine whether participants viewed the two treatments as equally credible [229]. Prior to randomization participants were asked to state their treatment preference (ICBT or CBGT). Assessments, including diagnostic interviews, were conducted before treatment, immediately after treatment, and six months after treatment. During treatment, the LSAS-SR was administered on a weekly basis. To ensure the integrity of the blinding procedure, participants were instructed not to mention which treatment they had received during the post-treatment and follow-up interviews. After completing the interviews, the assessing psychiatrists guessed allocation status for each participant.

3.2.2.4 Monitoring of treatment integrity

Treatment integrity of CBGT was ensured in three ways. First, a detailed treatment manual was used [22]. Second, group therapists received supervision throughout the trial by a licensed psychotherapist specialised in CBT for SAD. Third, all sessions were audio recorded and a random sample of 5 sessions was audited by a clinical psychologist with more than 10 years of experience in treating SAD with CBT. Using the Therapist Adherence Scale (TAS) developed by the originators of CBGT [230], all reviewed sessions were judged to have been conducted in accordance with the treatment manual.

3.2.2.5 Treatments

3.2.2.5.1 *Internet-based cognitive behavior therapy*

The ICBT employed in this study was the same as in Study I, with the only main difference being that the treatment duration was extended to15 weeks.

3.2.2.5.2 *Cognitive behavioural group therapy*

This treatment comprised an initial individual session followed by 14 group sessions over 15 weeks. The CBGT followed the protocol developed by Heimberg and Becker [22] as outlined in the Introduction section of the thesis.

3.2.2.6 Statistical analysis

The non-inferiority margin of the primary outcome measure LSAS was set at $\Delta 10$ points, which was based on clinical judgment and a review of the evidence of CBGT compared to credible control conditions for SAD. Meta-analytic reviews have estimated the lower bound of the 95% confidence interval (CI) of the between group effect size to 0.39 (Hedges'*g*) [231]. Assuming a standard variance of LSAS scores in our sample, this supported the use of 10 LSAS points as a non-inferiority margin. Test criterion for non-inferiority was that the lower bound of the 95% CI of the mean difference should fall within Δ. With 95% probability, the mean difference between ICBT and CBGT had to be smaller than 10 LSAS points. For the other continuous measures, the non-inferiority margin was set at Δ Cohen's *d*=0.5. Test criterion for non-

inferiority for these measures was that the lower bound of the 95% CI of between group effect sizes should fall within this range.

Main outcome continuous variables were analysed using a linear mixed effects model employing the restricted maximum likelihood method assuming a compound symmetry model as covariance structure [232]. To assess clinical significant improvement we used the criteria proposed by Jacobson and Truax [233]. The remaining analyses were carried out in the same fashion as in Study I. The sample size was considered satisfactory since power calculations showed that there was a chance slightly lower than 80% to detect a difference, given the non-inferiority criteria used and an alpha-level of .05. The main analyses were conducted in accordance with the ITT-principle.

3.2.3 Results

3.2.3.1 Attrition

At post-assessment, 63 of 64 (98%) participants in the ICBT group completed the self-report questionnaires and 59 (92%) participants attended the clinical assessment interview. The corresponding numbers in the CBGT group were 62 of 62 (100%) and 52 (81%).

3.2.3.2 Non-inferiority and effect sizes

At post-treatment and six month follow-up respectively, the 95% CI of the mean difference between the groups on LSAS was 0.68-17.66 and -2.5-15.69, favouring ICBT. This was well within the non-inferiority margin of 10 LSAS points for the lower bound. Analysis of the other continuous measures showed that all lower bounds of 95% CIs for between group effect sizes fell well within the non-inferiority margin of d=0.5. At post-assessment and follow-up, the between-group effect size range of social anxiety measures was 0.04-0.41, favouring ICBT.

3.2.3.3 Treatment effectiveness - primary outcome measure (LSAS)

At post-treatment, 35 (55%) of the participants (95% CI, 43%-67%) in the ICBT group were classified as responders compared to 21 participants (34%) in the CBGT group (95% CI, 22%-46%). At six-month follow-up, the corresponding number was 41 (64%) in the ICBT group (95% CI, 52%-76%) and 28 (45%) in the CBGT group (95% CI, 33%-58%). Mixed effects model analysis showed a significant effect of time, indicating improvement in both treatment groups (F=179.06; df=1,219; p<.001). There was no significant interaction of group and time for the primary outcome measure LSAS, indicating similar improvement across groups (F=1.58; df=2, 219; p=.21). As illustrated in Figure 4, there were continuous within group improvements throughout the trial on the LSAS-SR in both conditions.
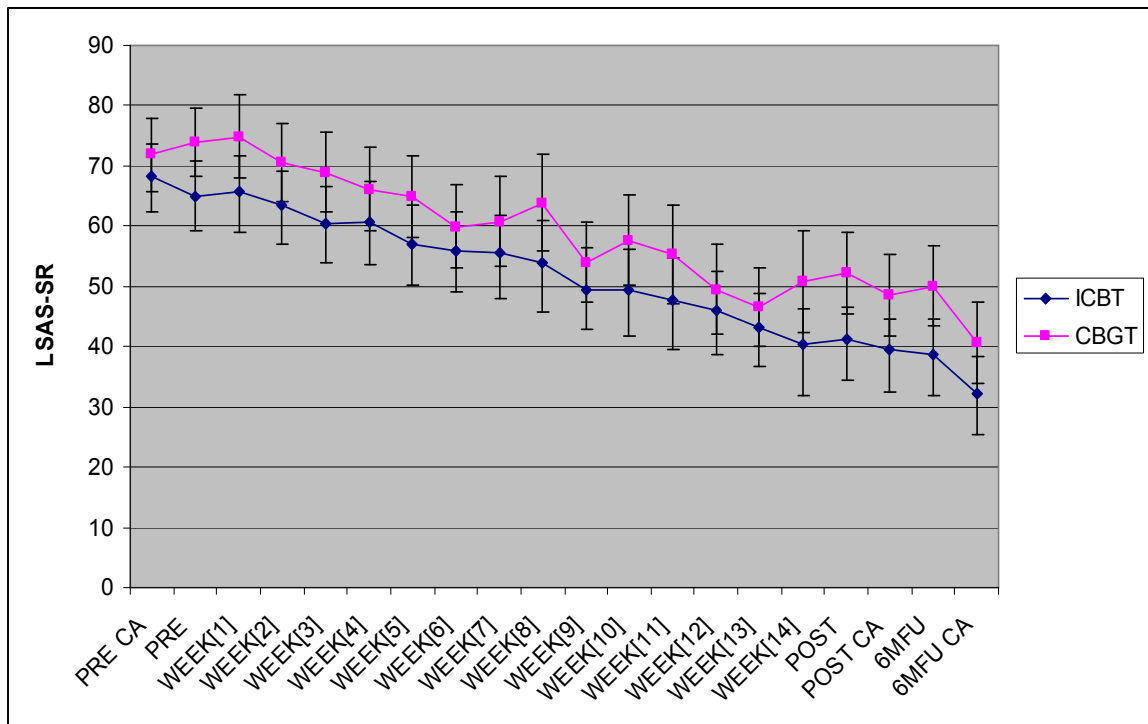
Figure 4. Weekly symptom change on the LSAS-SR

Abbreviations: ICBT, Internet-based Cognitive Behaviour Therapy; CBGT, Cognitive Behavioural Group Therapy; Pre, before treatment; Post, post-treatment; 6MFU, six months after treatment; CA, Clinician assessment; LSAS-SR, Liebowitz Social Anxiety Scale-self-report version. Note: Error bars represent 95 % CIs.

3.2.3.4   Treatment effectiveness - secondary outcome measures

3.2.3.4.1   Social anxiety

There was a significant effect of time on the SIAS and SPS (F=80.95 -83.39; df=2, p<.001). Mixed effects model analysis showed no significant interaction of group and time for these variables (F=0.30-0.48; df=2, 244; p=.62-.74).

3.2.3.4.2   Depression, general anxiety, anxiety sensitivity and quality of life

There was a significant effect of time on MADRS-S, BAI, ASI and QOLI (F=17.26-52.30; df=2, 227-245; p<.001). Analysis using mixed effects model yielded no significant interaction of group and time for these variables (F=0.26-1.30; df=2, 227-245; p=.28-.77).

3.2.3.4.3   Psychiatric diagnosis at each assessment point

Following treatment, 18 (31%) participants who had received ICBT no longer met diagnostic criteria for SAD (28% if considering dropouts as non-responders). The corresponding number for participants who underwent CBGT was 12 (23%; 19% if considering dropouts non-responders). At follow-up, 25 (46%) participants who had received ICBT (41% if considering dropouts non-responders) and 21 (40%) receiving CBGT (34% if considering dropouts non-responders) no longer met diagnostic criteria for SAD. At post-treatment and six month follow-up there was no significant difference in the prevalence of SAD between groups (χ^2=037-1.33, df=1, p=.25-.55).

3.2.3.4.4 Treatment credibility, blinding, adherence and treatment preference

Analysis of credibility ratings after one week of treatment showed that there was no significant difference in treatment credibility between treatment groups ($t_{(1, 110)}$=0.07, *p*=.95).

In four instances the blinding was broken. On two occasions participants accidentally mentioned their treatment allocation status to the assessor, and in other two occasions it was deemed necessary to break the blinding because of the need to assess increased depressive symptoms during treatment. There was no significant association between assessors' guess and actual treatment allocation (χ^2=0.27, df=1, *p*=.61), indicating successful blinding.

Prior to randomization participants were asked to state their treatment preference. Of 126 participants, 68 (54%) preferred ICBT and 58 (46%) CBGT. There was no difference between groups in terms of proportion of participants that received the preferred treatment (χ^2=0.77, df=1, *p*=.38).

In CBGT, the average number of attended sessions per participant was 9.40 (SD=4.87) out of a possible total of 15. Fifty participants in CBGT (81%) attended at least five sessions and 17 (27%) attended all sessions. The average number of completed modules in ICBT was 9.33 (SD=4.95) of 15. Fifty-one participants in ICBT (80%) completed at least 5 modules and 19 (29.7%) completed all modules.

3.2.3.4.5 Evaluation of therapist resources required for each treatment

On average, therapists delivering ICBT spent 5.5 minutes (SD=3.6) weekly per patient. The corresponding amount of time in CBGT was 50 minutes (2.5 h sessions with two therapists and 6 patients).

3.2.4 Discussion

The present study is the first study to demonstrate that ICBT can be as effective as CBGT in the treatment of SAD. The CIs of mean differences of the primary outcome measure fell well within the non-inferiority margin and between-group effect sizes were small but consistently favoring ICBT on the social anxiety measures. There was also a large proportion of participants who were classified as much improved or very much improved at post-treatment and follow-up in both treatment groups. The follow-up assessment indicated that treatment gains were sustained on all measures.

In trials assessing non-inferiority it is essential that the effect of the gold standard treatment is as effective as in previous trials. This was the case in the present study, where CBGT yielded effects in line with trials conducted by its originators [133]. Moreover, treatment effects for ICBT were equivalent to those reported in previous controlled trials [13, 14, 209, 211, 216]. As reduced therapist time is an important element of ICBT, a key finding in this study is that ICBT reduced therapist time per treated patient by 90% compared to CBGT. As outlined in the introduction of the thesis individual CBT may be even more effective than CBGT. However, as CBGT has been evaluated in more trials and is more established, we decided to use CBGT as the

benchmark treatment. Also, in a recent study by Andrews and colleagues, individual CBT did not show superiority over ICBT, albeit power was somewhat more limited compared to the present study [207].

3.3 STUDY III. FIVE-YEAR FOLLOW-UP OF INTERNET-BASED COGNITIVE BEHAVIOUR THERAPY FOR SOCIAL ANXIETY DISORDER

3.3.1 Context and aims

While several studies have shown that conventional CBT for SAD produces long-term improvements up to five years after treatment [234-237], nearly all studies on ICBT have had a follow-up period of one year or shorter. The one exception is a study where participants receiving ICBT not only maintained their treatment gains but were further improved at a 2.5-year follow-up [238]. This is in line with the notion that reduced anxiety following CBT to a large extent is contingent on repeated exposure [239]. The aim of the present study was to investigate the effects of ICBT for SAD five years after treatment. No previous study has investigated if the effect of ICBT persists over this long period of time. We hypothesised that treatment gains would be sustained on measures of social anxiety, depressive symptoms, general anxiety and quality of life.

3.3.2 Methods

3.3.2.1 Design

This was a follow-up study assessing 80 participants who had received ICBT for SAD within the context of an RCT (Study I). In the original RCT, participants were randomised to ICBT (n=40) WLC (n=40) with equal probability (the bibliotherapy arm was not included in this study). Following treatment and post-assessment, participants in the WLC group were crossed over to treatment and the group is henceforth denoted WL-ICBT. Thus, both groups had received ICBT at one-year follow-up. As the ICBT and WL-ICBT groups received treatment at different time points, results are reported separately for the two groups.

3.3.2.2 Recruitment and treatment

See Study I.

3.3.2.3 Outcome measures

The primary outcome measure was the LSAS-SR [221]. We also used the SIAS [222], and the SPS [222] as complementary measures of social anxiety. In addition, the MADRS-S [219], the BAI [223] and the QOLI [224] were used as secondary measures to assess depressive symptoms, general anxiety, and quality of life, respectively.

3.3.2.4 Clinical assessment interview

The SCID-I-RV [220] was used to establish whether participants met diagnostic criteria for SAD at five-year follow-up. Global improvement was measured by the Clinical Global Impression Improvement Scale [CGI-I; 240]. In addition, information about current and earlier psychological and pharmacological treatments was obtained. Finally, participants were asked to rate to which extent they attributed their improvement/current state to ICBT.

3.3.2.5 Procedure

The clinical assessment interview was performed by a clinical psychologist with more than five years of experience in working with structured diagnostic assessments. The interview was conducted by telephone, which has been shown to be a reliable way of assessing psychiatric symptoms [241, 242].

3.3.2.6 Statistical analysis

While data were analysed on ITT basis, last observation carried forward to handle missing data was not applied as that might have exaggerated the degree to which gains were sustained. Instead, estimated parameters were obtained using a mixed-models approach. [232]. The following formula was used for converting standard errors to standard deviations: $SD = SE(\sqrt{n})$. As all participants received ICBT, the main analyses entailed no between group comparisons. Nominal data were analyzed with McNemar's test of change.

3.3.3 Results

3.3.3.1 Attrition

Of 80 participants, 71 (89%) attended the clinical assessment interview and 64 (80%) completed the LSAS-SR, SIAS, SPS, MADRS-S, BAI and QOLI. There were no statistical significant differences between participants who did not provide follow-up data and those who did regarding gender ($\chi^2=0.39$, df=1, $p<.39$), age, and social anxiety at baseline or at one-year follow-up ($t_{(1, 67-78)}=0.40-1.74$, $p<.68-.09$).

3.3.3.2 Social anxiety measures

Figure 5 displays changes on the primary outcome measure LSAS-SR across assessment points. The effect sizes at five-year follow-up in comparison to baseline were large on the LSAS-SR, $d=1.3$ (95% CI 0.8-1.8) in the ICBT group and $d=1.4$ (95% CI 0.9-1.9) in the WL-ICBT group. Mixed effect models analysis showed a significant effect of time on the primary outcome measure LSAS-SR, as well as on the SIAS and SPS ($F=16.05-29.20$; df=3, 98-102; $p<.001$).

Pairwise comparisons showed that participants in both groups were significantly improved from baseline to one- and five-year follow-up on all social anxiety measures ($F=15.10-90.05$; df=1, 33-38; $p<.001$). Both groups were further improved at one-year follow-up compared to post-assessment *($F=7.43-40.42$; df=1, 34-35; $p<.01-.001$)*. There were no significant changes on the LSAS and SPS between one- and five-year follow-up ($F=0.22, 0.93$; df=1, 28, 32; $p<.64-.13$). In the WL-ICBT group, but not in the ICBT group, participants were further improved on the SIAS at five-year follow-up compared to one-year follow-up ($F=7.85$; df=1, 29; $p<.01$).
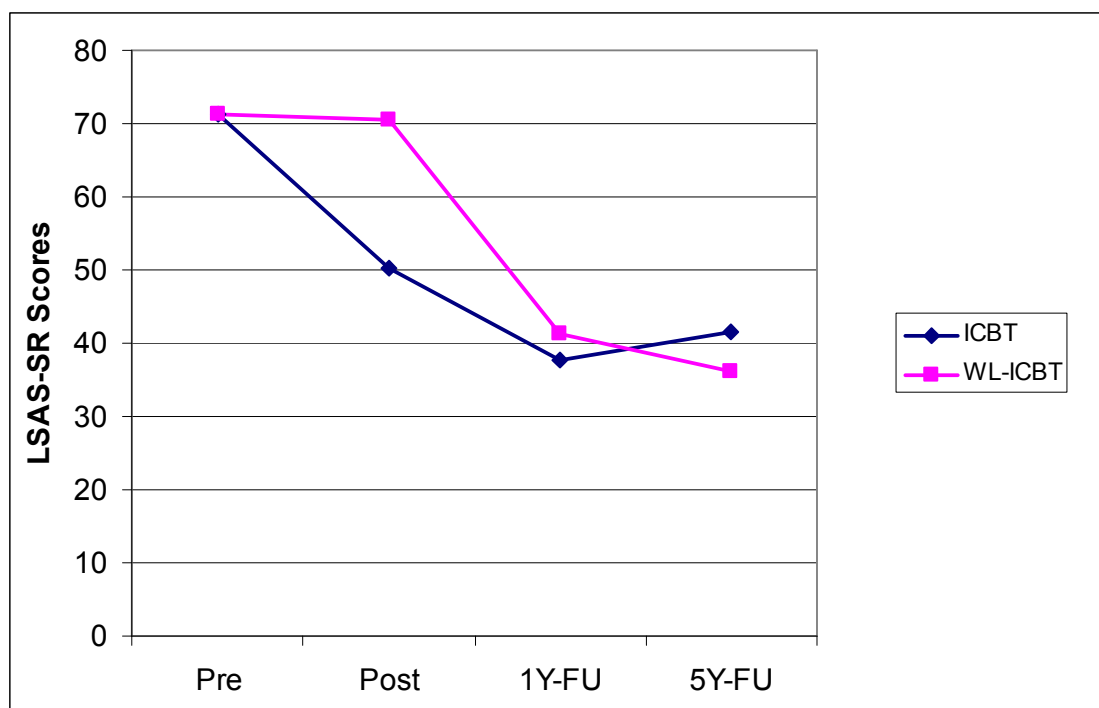
Figure 5. Improvement course on the primary outcome measure LSAS-SR during the follow-up period.

Abbreviations: ICBT, Internet-based Cognitive Behaviour Therapy; WL-ICBT, Waiting list followed by Internet-based Cognitive Behaviour Therapy; Pre, before treatment; Post, post-treatment; 1Y-FU, one year after treatment; 5Y-FU, five years after treatment; LSAS-SR, Liebowitz Social Anxiety Scale-Self-Report.

3.3.3.3 Depressive symptoms, general anxiety and quality of life

Mixed effect models analysis showed a significant effect of time on the MADRS-S, BAI and QOLI (F=4.64-9.78; df=3, 97-104; p<.01-.001). Pairwise comparisons showed that participants in both groups were significantly improved from baseline to one- and five-year follow-up on MADRS-S, BAI and QOLI (F=4.7-30; df=1, 32-40; p<.04-.001). The WL-ICBT was further improved at one-year follow-up compared to post-assessment on these measures (F=12.12-13.83; df=1, 34, 35; p<.001), whereas the ICBT group was not (F=0.36-3.09; df=1,35-37; p<.55-.09). There were no changes on these measures from one-to five-year follow-up (F=0.01-3.80; df=1, 28, 33; p<.94-.06).

3.3.3.4 Clinical assessment interview

3.3.3.4.1 Global improvement and diagnostic assessment

At five-year follow-up, 24 participants (60%) in the ICBT group and 27 (67.5%) in the WL-ICBT group were considered very much or much improved, i.e. responders. At five-year follow-up, 19 participants (48%) in both groups no longer met diagnostic criteria for SAD according to the clinician assessment (counting dropouts as non-responders). McNemar's test showed that this was a statistically significant change compared to baseline (p<.001).

46

3.3.3.4.2 *Participants' attribution of improvement*

Participants were asked to rate to which extent they attributed their improvement to the ICBT on a Likert-scale from 0-100 (0=any improvement is completely unrelated to ICBT; 50=any improvement is equally due to ICBT and other causes; 100=any improvement is completely due to ICBT). In the ICBT group, the average score was 60.3 (SD=26.9) and the corresponding WL-ICBT score was 61.8 (SD=25.9).

3.3.3.4.3 *Other psychological and psychotropic treatments received since ICBT*

At five-year follow-up, four (10%) participants in the ICBT group had received some form of psychological treatment (all reasons included) after ICBT. The corresponding number in the WL-ICBT group was seven (17.5%). One participant (2.5%) in the ICBT group was taking psychotropic medication (SSRI) at the time of the five-year follow-up assessment, although four participants (10%) had started and discontinued psychotropic medication at some point during the follow-up period (all SSRIs). In the WL-ICBT group, the corresponding numbers was 3 (7.5%) and 5 (12.5%), respectively (all SSRIs).

3.3.4 Discussion

The aim of this study was to evaluate the five-year effect of ICBT for SAD by assessing participants receiving treatment in Study I. The results showed that improvements on measures of social anxiety at one-year follow-up were sustained five years after treatment. Overall, effect sizes were large on measures of social anxiety. Improvements regarding depressive symptoms, general anxiety and quality of life were also sustained at five-year follow-up. The results of this study indicate that participants receiving ICBT for SAD are moderately improved immediately following treatment, but make further improvements within the following year. Improvements made at one-year follow-up are, in turn, long-term enduring.

The effect sizes in this study are in line with those reported in studies investigating the long-term effects of conventional CBT for SAD [235, 243]. The major strength of this study is that attrition rates were low making the generalizability of the findings high. Furthermore, participants attributed their improvement to ICBT to a large extent and few had commenced other forms of psychological or psychotropic treatments after completing ICBT. Taken together, this suggests that the reduction of social anxiety observed at five-year follow-up was largely an effect of ICBT.

3.4 STUDY IV. COST-EFFECTIVENESS AND COST-UTILITY OF INTERNET-BASED COGNITIVE BEHAVIOUR THERAPY VS. COGNITIVE BEHAVIOURAL GROUP THERAPY FOR SOCIAL ANXIETY DISORDER: RESULTS FROM A RANDOMISED CONTROLLED TRIAL

3.4.1 Context and aims

Several features of SAD contribute to making it an economic burden from a societal perspective. It is highly prevalent [8], has an onset in early adolescence [6], and is associated with academic underachievement and an increased risk of unemployment [3, 4]. As ICBT requires a limited amount of therapist resources, often less than 10 minutes weekly per patient [12, 203], it has the potential of being a more cost-effective treatment than conventional CBT. To date, no study has prospectively investigated the economic impact and cost-effectiveness of ICBT or CBGT for SAD from a societal perspective. The aim of the present study was to investigate the economic impact of ICBT compared to CBGT for SAD from a societal perspective within the context of an RCT. We hypothesised that the treatments would generate significant and equivalent societal cost reductions. In addition, we expected ICBT to be more cost-effective due to lower costs of treatment.

3.4.2 Methods

3.4.2.1 Trial design

This was a prospective cost-effectiveness analysis study adopting a societal perspective. The data were collected from the participants receiving ICBT (n=64) or CBGT (n=62) in the RCT of Study II.

3.4.2.2 Assessment of costs

Health economic cost data were obtained using the Trimbos and Institute of Medical Technology Assessment Cost Questionnaire for Psychiatry [TIC-P; 244]. The human capital approach was used which means that monetary losses associated with work loss and work cutback were based on the average gross earning in Sweden for the duration of the sick leave [245]. The direct medical costs associated with ICBT and CBGT were mainly represented by the costs of therapists. In this study, the tariff of visits to licensed clinical psychologists was used when estimating costs for both treatments. The time the therapists spent on treating the participants were registered and multiplied with this tariff.

3.4.2.3 Clinical assessments and treatments

The primary outcome measure was the LSAS [LSAS; 226, 246]. The procedure and other assessment instruments used are described in Study II. We used the EuroQol [EQ-5D; 247] to assess quality of life from a health perspective. Treatment interventions were ICBT and CBGT as presented in Study II.

3.4.2.4   Statistical analysis

Analyses were conducted in accordance with the ITT-principle using LOCF. Costs were assessed at pre-treatment, post-treatment and six month follow-up. All costs were extrapolated to a six month period. Since the cost data were non-normally distributed, p-values were estimated using a general linear model with bootstrap analysis (5,000 replications) [248]. Incremental cost effectiveness ratios (ICERs) were estimated using the following formula:

$$\frac{\Delta^{C1} - \Delta^{C2}}{\Delta^{E1} - \Delta^{E2}}$$

In the formula, C1–C2 is the difference in costs between ICBT and CBGT conditions and E1–E2 refers to difference of the average effectiveness of the two conditions [245]. The costs, including all medical and non-medical costs, of the participants in the ICBT condition were subtracted from the costs of the participants in the CBGT condition. This difference was then divided with the subtracted effects (in this case improvement of social anxiety assessed with the LSAS). This procedure was bootstrapped 5,000 times, generating an estimated figure of the treatment groups' incremental costs in relation to their incremental health benefit. A cost-utility analysis was also conducted, i.e. an analysis identical to cost-effectiveness analysis with the exception that the cost of an additional quality adjusted life year [QALY; 199] is calculated. Finally, data robustness was tested in sensitivity analyses. This was done by repeating the analysis while increasing the estimated intervention cost of ICBT. First, $200 was added corresponding to a scenario of reduced production capacity of ICBT due to poorer treatment planning rendering longer average time spent in the system [249]. Second, $600 was added to the cost of ICBT corresponding to the cost of ICBT during the first year of providing the service, thereby including all developmental costs and costs of establishing the treatment unit.

3.4.3 Results

3.4.3.1   Costs

Participants in both treatments significantly reduced their gross total costs at six-month follow-up in comparison to pre-treatment ($t_{(61-63)}$=2.00-2.38, $p<.02$-05). During this period the gross total cost reduction was $1885 in the ICBT group and $2810 in the CBGT group. The indirect non-medical costs were also reduced in both groups at follow-up, ($t_{(61-63)}$=2.21-2.45, $p<.02$-03). There were however no significant reductions of gross total costs at post-treatment compared to pre-treatment ($t_{(61-63)}$= 1.89-1,11), $p<.07$-.28) There were no significant between group differences in any of the cost domains at post-treatment or follow-up ($t_{(1, 124)}$=0.13-0.16, $p<.16$-90). The intervention costs per participant were estimated to $464 (SD=128) for ICBT and $2687 (SD=0) for CBGT ($t$=137, df=1,124, p<0.001). The difference in costs of ICBT and CBGT was attributable to the differences in therapist time required. On average, therapists delivering ICBT spent 5.5 minutes (SD=3.6) weekly per patient. The corresponding amount of time in CBGT was 50 minutes (2.5 h sessions with two therapists and 6 patients). Taking nonattendance into consideration, this number would have been even higher in the CBGT condition.

3.4.3.2 Cost-effectiveness

At follow-up, the incremental cost effectiveness ratio (ICER) was -1335/ 0.19 = -7046 favouring ICBT over CBGT. This means that that each incremental clinical significant improvement on LSAS for participants in ICBT relative to CBGT generated a societal earning of $7046. This was because the total net costs were lower in the ICBT condition compared to the CBGT condition and that clinical significant improvements in social anxiety were slightly more likely to occur in the ICBT condition. Figure 6 presents the scatter of simulated ICERs across the four quadrants of the ICER plane. A majority of the simulated ICERs are located in the south east quadrant (79.5%) compared to 19.0% in the north east quadrant, indicating that ICBT is cost-effective compared to CBGT. The same data are used to plot the acceptability curve in Figure 7, which also displays the two sensitivity analyses curves. The curve indicates that ICBT has an 81% probability of being cost-effective if society were willing to pay $0 for one additional improved patient with SAD. If society were willing to pay $3000 for one case of improvement, the probability of ICBT being cost-effective would increase to 89%.
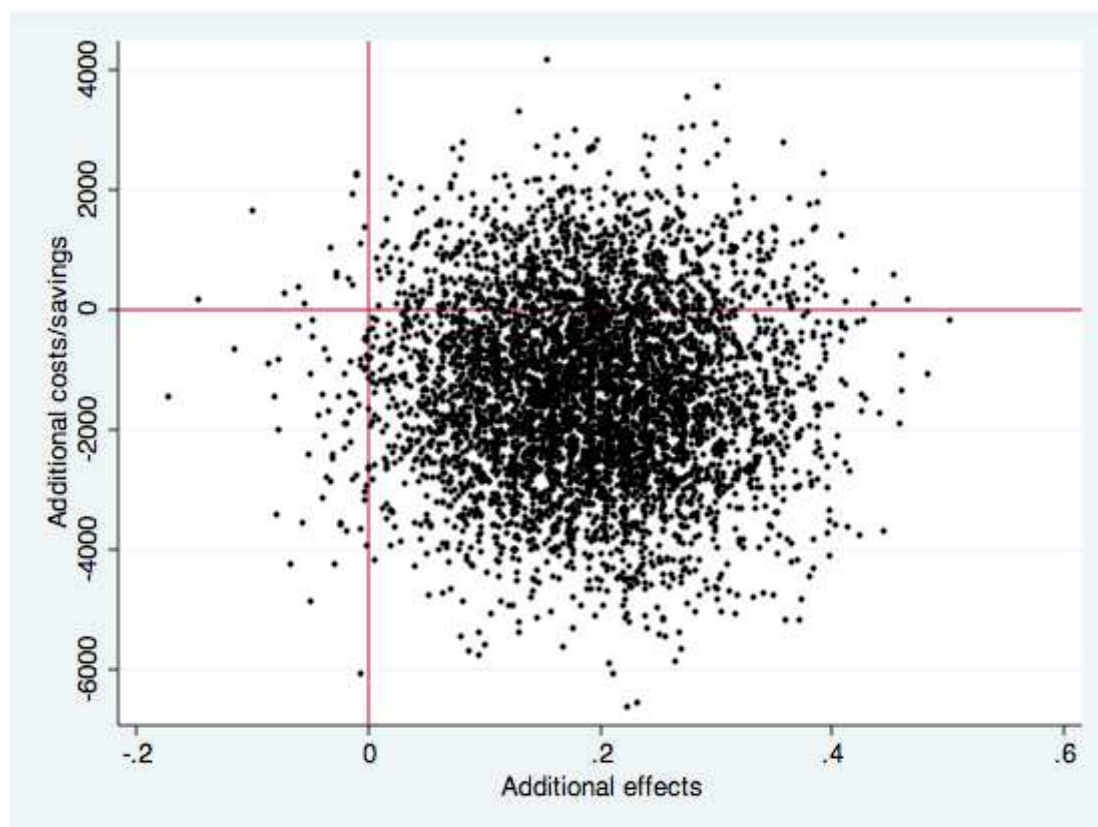

Figure 6. Cost-effectiveness plane comprising 5000 boot strapped ICERs comparing ICBT to CBGT.

Abbreviations: ICBT, Internet-based cognitive behaviour therapy; CBGT, cognitive behavioural group therapy.
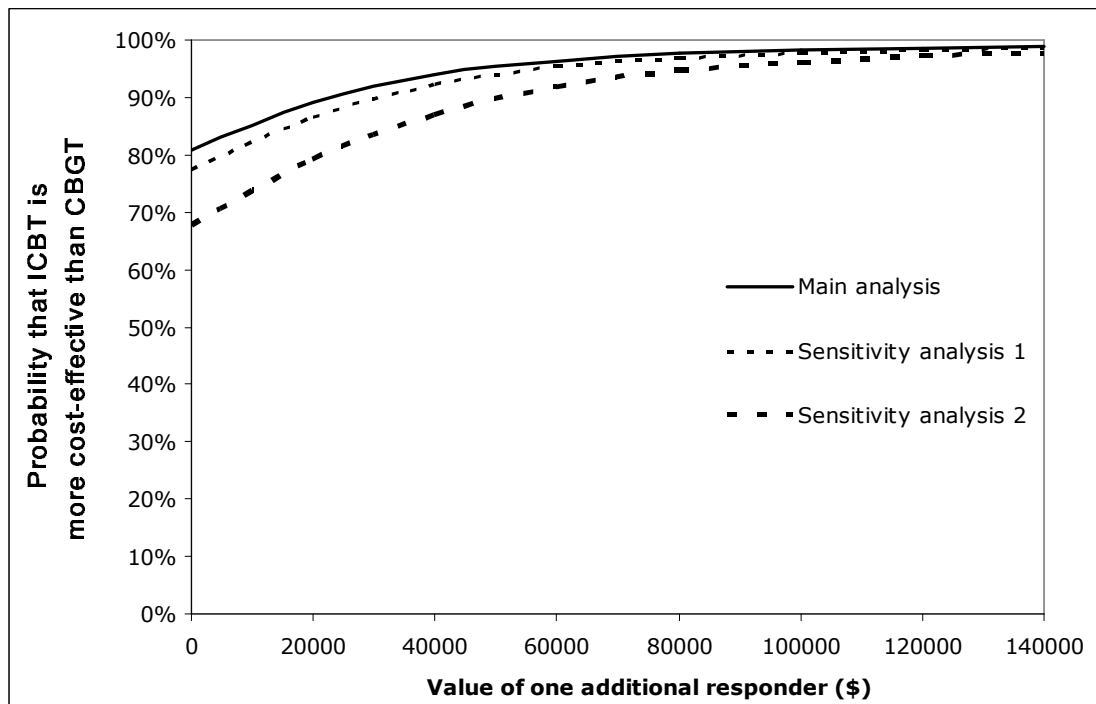
50

Figure 7. Cost-effectiveness acceptability curve for ICBT compared to CBGT.

Note: Solid line (main analysis) represents probability of ICBT being cost-effective under regular circumstances; Sensitivity analyses 1 represents the acceptability curve if $200 (low productivity scenario) is added to the cost of ICBT and Sensitivity analysis 2 if $600 is added (first year of implementation). Abbreviations: ICBT, Internet-based cognitive behavior therapy; CBGT, cognitive behavioural group therapy.

3.4.3.2.1 Cost-utility analysis

Participants in both treatment conditions reported higher quality of life at post-treatment ($t_{(61-63)}$=3.88-2.16, $p<.001$-.03) and six-month follow-up ($t_{(61-63)}$=3.14-3.46, $p< .001$-.01) compared to pre-treatment according to the EQ-5D. At follow-up, the cost-utility ICER was -1335 / 0.075 = -17 823. This meant that one additional QALY generated a societal earning of $17 823 when comparing ICBT to CBGT**.** The bootstrapped ICER data indicated that ICBT has an 81% probability of being cost-effective if society would pay $0 for one gained QALY. If society were willing to pay $40,000 for one additional QALY, the probability of ICBT being cost-effective would remain about the same (79%).

3.4.3.2.2 Sensitivity analyses

As shown in Figure 7, ICBT would remain the most cost-effective treatment even if increasing the cost of ICBT corresponding to a) a scenario of low productivity or b) the costs of treatment in the first year of implementation.

3.4.4 Discussion

As expected, both treatments generated a substantial reduction of societal costs. The hypothesis that ICBT would be a cost-effective treatment alternative in comparison to CBGT, was also supported. This was a result of equivalent effects of the treatments in terms of reducing societal costs, social anxiety and improving quality of life, but

significantly lower intervention costs for ICBT compared to CBGT. This difference was primarily due to less therapist time required in ICBT. The sensitivity tests showed that the findings were robust in the sense that ICBT would be the most cost-effective treatment even if using conservative intervention cost estimates. Although ICBT was more cost-effective than CBGT it is important to note that both treatments generated large cost reductions and considering the chronicity of SAD [7, 250], it is highly likely that both treatments generate societal cost savings compared to no treatment. These results are interesting from a health care policy perspective as they show that the savings generated exceed the cost of treatment in a remarkably short time frame. This implies that society as a whole would be financially strengthened by making CBT for SAD more accessible.

A limitation of the study was that the estimates of costs were based on TIC-P, which is a self-report questionnaire and thereby potentially less accurate compared to data collected directly from public registers. This risk, however, is likely to be equal across treatments, making it unlikely that it could account for between group differences and empirical evidence suggests that economic data obtained by self-report is equally valid compared to register collected data [251]. In spite of this limitation, the results of the present study are important as they show that CBT for SAD in general and ICBT in particular, generate substantial societal cost reductions.

3.5 STUDY V. CLINICAL AND GENETIC OUTCOME DETERMINANTS OF INTERNET- AND GROUP-BASED COGNITIVE BEHAVIOUR THERAPY FOR SOCIAL ANXIETY DISORDER

3.5.1 Context and aims

A substantial proportion (25-50%) of those receiving ICBT and cognitive behavioural group therapy (CBGT) do not respond sufficiently well to treatment [133, 186]. Under these circumstances, the identification of outcome predictors and moderators could facilitate: a) reduced dropout rates and number of treatment failures [161, 162], and b) individually tailored treatments [161, 163].

The general aim of the present study was to investigate demographic, clinical, therapy processes related and genetic predictors and moderators of treatment outcome of ICBT compared to CBGT. Specific aims were to investigate predictors and moderators of a) the main continuous outcome measure of social anxiety, and b) fulfilment of diagnostic criteria for SAD. Finally, we aimed to identify subgroups likely to achieve clinical significant improvement by producing a clinical decision tree entailing optimal predictor and sub predictor cut-off points. We expected that variables indicating strong social support, less psychiatric comorbidity, treatment adherence and receiving the preferred type of CBT would predict treatment response. In addition, we hypothesised that non S-allelic carriers of the serotonin transporter gene promoter (5-HTTLPR) polymorphism, and non-met allelic carriers of the catechol-O-methyltransferase gene polymorphism (COMTvalmet158) and the brain derived neurotrophic factor (BDNFval66met) gene polymorphism would have a superior treatment response.

3.5.2 Method

3.5.2.1 Trial design, recruitment and treatment interventions

This was a study assessing predictors and moderators within the context of a parallel group trial with unrestricted randomisation in 1:1 ratio (Study II of the thesis). Participants were 126 persons with SAD who participated in Study II. See Methods in Study II for inclusion criteria and recruitment. The treatments were ICBT and CBGT.

3.5.2.2 Main dependent variables

The primary outcome measure was the clinician administered LSAS [246]. Clinical significant improvement was based on the LSAS using the criteria proposed by Jacobson & Truax [233]. The SCID-I-RV was used to establish SAD diagnosis.

3.5.2.3 Potential predictors and moderators

3.5.2.3.1 Demographic characteristics and personality traits

Demographic data were collected in the diagnostic interviews. To assess personality traits, we used the Swedish Scales of Personality [SSP; 252].

3.5.2.3.2 Clinical characteristics and therapy process related measures

In the diagnostic interviews, we used the SCID-II [253] to assess avoidant personality disorder and MINI to assess axis I disorders other than SAD. Data regarding age of onset and severity of social anxiety were also collected in these interviews. Continuous assessment of depressive symptoms and general anxiety was conducted using the MADRS-S and the BAI respectively.

The Credibility scale was administered to determine whether participants viewed the respective treatment as credible and likely to be effective. Prior to randomisation participants were asked to state their treatment preference (ICBT or CBGT). Whether participants received their preferred treatment or not was used as a potential predictor/moderator. Treatment adherence was defined as attending at least five group sessions (CBGT) or completing at least five modules (ICBT).

3.5.2.3.3 Genetic analysis

DNA extraction from whole blood was performed using standard methods [254]. For the biallelic 5-HTTLPR, two fragments, 336b (short) and 379 bp (long), were amplified by polymerase chain reaction (PCR), amplified on Biorade Tetrade (BIORAD, Hercules, CA, USA). To genotype COMTval158met (rs4680) and the BDNFval66met (rs6265), we used the Taqman® allelic discrimination assay (5' nuclease assay, performed on an ABI HT7900 (Applied Biosystems, Foster City, CA)). All genotypes were determined in duplicates

3.5.2.4 Statistical analysis

Three types of data analyses were performed, each corresponding to a specific aim. We used two types of regression analyses. In these analyses, the two-step approach proposed by de Graaf and co-workers was adopted [167]. This meant identifying significant univariate predictors, and subsequently adding those into a final multivariate model. Social anxiety measured by the LSAS was analysed within a linear regression framework. For each variable a regression model was built using LSAS scores as dependent variable and forced entry as regression method. Each model contained LSAS baseline values, the potential predictor variable, treatment condition (ICBT/CBGT), and the interaction term of predictor and treatment condition. Prior to analyis data were standardised and mean centered. All dependent variables were assessed at six-month follow-up. As suggested by Holmbeck, a variable is a predictor if it has a main effect on the dependent variable and a moderator if there is a significant interaction effect, i.e. predictor * treatment condition [255].

The second type of analysis performed was logistic regression using diagnosis of SAD as dependent variable applying the same model building approach. Finally, signal detection analysis based on recursive partitioning was performed yielding receiver operator characteristics (ROC) of subgroups with high and low chance of achieving clinical significant improvement [256, 257]. Signal detection is an iterative process of splitting the sample in two groups based on the optimal predictor cut-offs. For each node in the tree, odds ratios were calculated. Missing LSAS data was handled by substituting the clinician score with the LSAS-SR score. Participants not attending the

diagnostic interviews were considered having SAD, except if they scored <15 on the LSAS-SR, which ensured very high negative predictive value [258].

3.5.3 Results

3.5.3.1 Predictors and moderators of social anxiety assessed by the LSAS

Parameter estimates of significant predictors and moderators of the final linear regression analysis are presented in Table 4.

3.5.3.1.1 Demographic variables and personality

The initial linear regression analyses showed that employment status, educational level, having children, and quality of life (QOLI) were significant predictors (i.e., working full time, having attended college, having children and a higher QOLI score predicted better outcome). The personality traits adventure seeking and impulsiveness were significant moderators, meaning that high levels of these traits were associated with less social anxiety in CBGT but not in ICBT. In the final model, the predictors employment status and having children remained significant.

3.5.3.1.2 Clinical characteristics

Level of depressive symptoms (MADRS-S) was found to be a significant predictor in the initial analysis (i.e. less depressive symptoms predicted better outcome). Comorbid depression and general anxiety measured by the BAI were significant moderators, showing that absence of depression and lower general anxiety was associated with lower LSAS scores in ICBT but not in CBGT. Type of SAD (generalised or not) did not moderate outcome. The final model retained depressive symptoms as a predictor and general anxiety as a moderator.

3.5.3.1.3 Process related measures

Treatment credibility and treatment adherence were significant predictors (i.e. higher credibility scores and completing at least five sessions or modules predicted better outcome). Computer skills did not moderate treatment effects. Both predictors remained significant in the final model.

3.5.3.1.4 Genetic factors

No genetic polymorphisms were significant predictors or moderators. Thus, no genetic data were included in the final model.

Table 4. Linear regression presenting the final model using LSAS scores at six-month follow-up as dependent variable.

Variable	B	SE	β	P-value
Model				
R=.74		17.12		<.001
R^2=.54				
Adj R^2=.52				
Predictors				
Employment status (working full time)	-5.30	1.68	-.22	<.01
Having children	-6.56	3.17	-.13	<.05
Treatment adherence (Yes)	-14.20	4.05	-.23	<.001
Depressive symptoms (MADRS-S)	2.96	1.70	.12	<.09
Treatment Credibility (C-Scale)	-6.07	1.68	-.25	<.001
LSAS baseline	10.01	1.65	.41	<.001
Moderators				
General Anxiety (BAI)	5.64	1.59	.23	<.001

Abbreviations: QOLI, Quality of life inventory; MADRS-S, Montgomery Åsberg Depression Rating Scale-Self report; C-Scale, Credibility Scale; LSAS, Liebowitz Social Anxiety Scale; BAI, Beck Anxiety Inventory

3.5.3.2 Predictors and moderators of diagnostic status (having SAD or not)

Table 5 presents parameter estimates of significant predictors found in the final logistic regression analysis.

3.5.3.2.1 Demographic variables and personality

The initial logistic regression analyses showed that having children, higher age and lower stress susceptibility predicted better outcome. The personality trait impulsiveness was a significant moderator, meaning that a higher level of impulsiveness was associated with absence of SAD diagnosis in CBGT but not in ICBT. In the final model age remained a significant predictor.

3.5.3.2.2 Clinical characteristics

Number of years with SAD, depressive symptoms as assessed by the MADRS-S and comorbid depression were found to be significant predictors (i.e. more years with SAD, less depressive symptoms/ absence of depression predicted better outcome). General anxiety measured by the BAI was a significant moderator, showing that lower general anxiety was associated with absence of SAD diagnosis in ICBT but not in CBGT. Type of SAD (generalised or not) did not moderate outcome. The final model retained age and comorbid depression as predictors and general anxiety as a moderator.

3.5.3.2.3 Process related measures

Higher treatment credibility and adhering to treatment predicted better outcome. Computer skills did not moderate treatment effects. Treatment adherence remained significant in the final model.

3.5.3.2.4 Genetic factors

As in the linear regression analysis, no genetic polymorphisms were significant predictors or moderators. Thus, no genetic data were included in the final multivariate model.

Table 5. Logistic regression presenting the final model using SAD diagnosis (yes/no) at six-month follow-up as dependent variable.

Variable	Chi-2	-2 Log Likelihood	Cox & Snell R2	Nagelkerke R2	P-value
Model					
Omnibus Test (df=4)					<.001
Chi-2, 34.63		134.61	.24	.33	
	B	**SE**	**Wald**	**Exp (B)**	
Predictors					
Age	.50	.21	5.49	.20	<.01
Comorbid depression	2.26	.82	7.58		<.02
Treatment adherence (Yes)	-1.61	.62	6.65	.20	<.01
Moderator					
General Anxiety (BAI)	-1.09	.40	7.56	.34	<.01

Abbreviations: SAD, Social Anxiety Disorder; BAI, Beck Anxiety Inventory; Exp, exponentiated based on the natural logarithm

3.5.3.3 Signal detection analysis of clinical improvement and decision tree

The analysis yielded a model with three interacting predictors comprising treatment adherence, heredity of SAD, and depressive symptoms assessed by MADRS-S as best predictors (χ^2=8.56-23.02, df=1, *ps*<.01). The subgroup with highest chance of achieving clinical improvement was that comprising participants adherent to treatment without heredity of SAS. The lowest chance of clinical improvement was found for those who a) did not adhered to therapy, or b) adhered to therapy but had heredity of SAD and were moderately to severely depressed. Figure 8 displays the clinical decision tree including optimal cutoff points. The odds ratio range was 3.84-16.00 indicating moderate effect of the predictors [259].
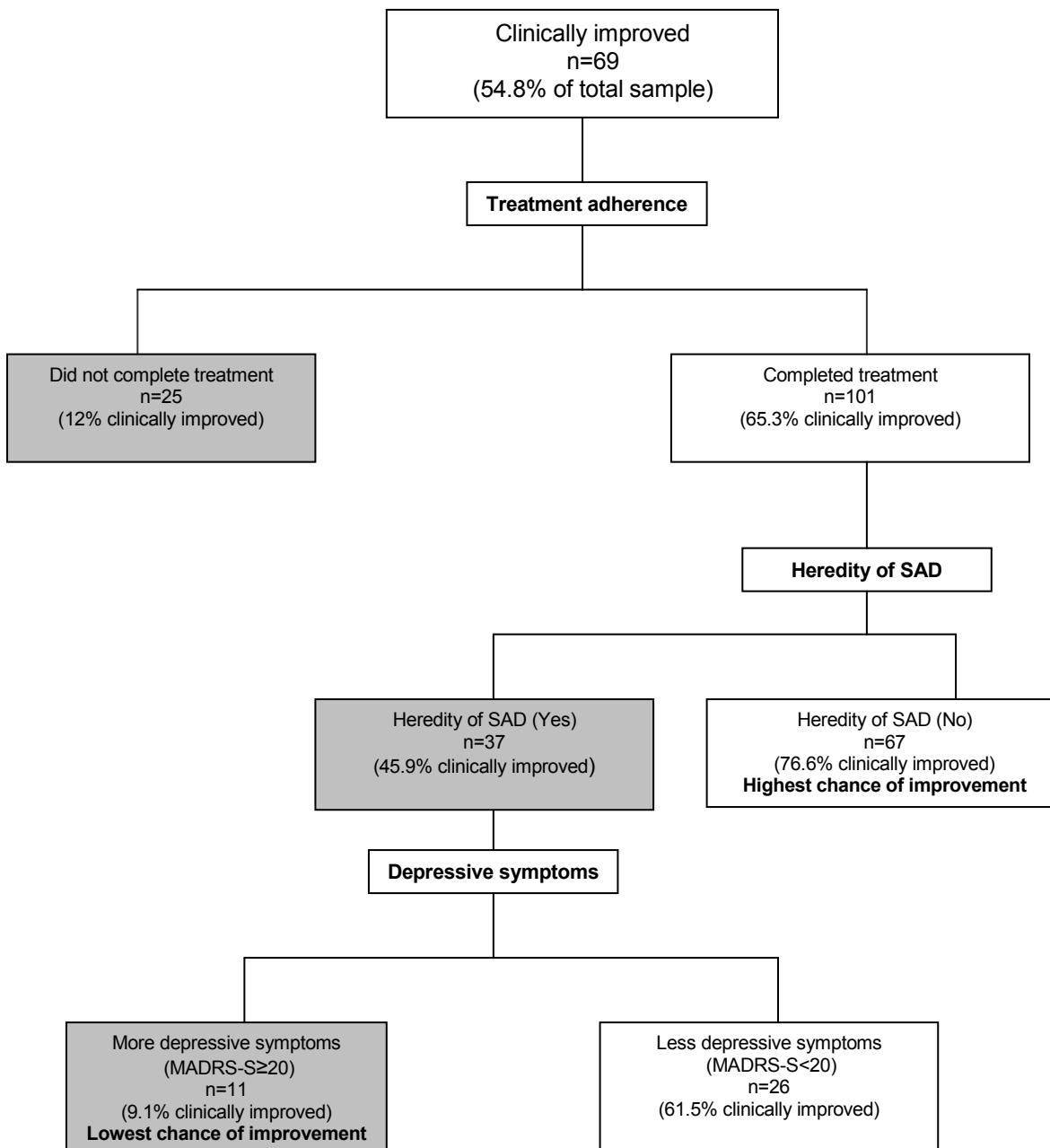
```
                         ┌─────────────────────────┐
                         │    Clinically improved   │
                         │           n=69           │
                         │  (54.8% of total sample) │
                         └────────────┬─────────────┘
                                      │
                            ┌──────────────────┐
                            │ Treatment adherence │
                            └─────────┬────────┘
                    ┌─────────────────┴─────────────────┐
        ┌───────────────────────┐           ┌───────────────────────┐
        │ Did not complete       │           │  Completed treatment   │
        │ treatment              │           │         n=101          │
        │ n=25                   │           │ (65.3% clinically      │
        │ (12% clinically        │           │  improved)             │
        │  improved)             │           └───────────┬───────────┘
        └───────────────────────┘                        │
```


Figure 8. Clinical decision tree based on signal detection analysis.

Receiver operator characteristics (ROC) for predictor Treatment adherence: a) Sensitivity, 96.7%, b) Specificity, 38.6%; ROC for predictor Heredity of SAD, a) Sensitivity, 74.2%, b) Specificity, 57.1%; ROC for predictor Depressive symptoms, a) Sensitivity, 94.1%, b) Specificity, 50.0%.

3.5.4 Discussion

To my knowledge, this is the first trial aiming to identify demographic, clinical and genetic predictors and moderators of ICBT relative to traditional CBT for SAD. In both treatments having children, working full time, having less depressive symptoms, treatment adherence and higher expectancy of treatment effectiveness were significant predictors of six-month outcome. This was the case both when assessing outcome with the LSAS and when using SAD diagnosis as dependent variable. Contrary to our

hypothesis, none of the investigated genetic polymorphisms predicted treatment outcome. The final linear regression model explained more than 50% of the variation of the main outcome measure LSAS at follow-up, suggesting that it might be highly valuable for the clinician to assess these factors when planning and evaluating treatment.

The primary limitation of this study common to most RCTs is the inherent restriction in terms of predictors and moderators as those likely to have the strongest impact on outcome are part of the exclusion criteria. Nevertheless, this trial was an effectiveness trial which aimed to include patients normally seen in regular psychiatric settings. This means that there were relatively few restrictions, e.g. comorbid psychiatric diagnosises were allowed. An additional limitation is that power to detect predictors and moderators with small effect sizes was limited. However, predictors with very small effects are often of limited clinical relevance.

4 CONCLUDING DISCUSSION

4.1 PRIMARY FINDINGS

This thesis provides new evidence clearly demonstrating that Internet-based cognitive behaviour therapy (ICBT) for social anxiety disorder (SAD) is an effective treatment in an experimental as well as in a clinical setting. The studies of this thesis have also shown that effect of ICBT is enduring over at least half a decade and that the treatment is cost-effective in comparison to conventional CBT. Also, new clinically useful knowledge regarding determinants of outcome is provided. In the following section, the results are discussed in greater detail.

4.1.1 Efficacy of ICBT for SAD

The findings of the present thesis indicate that ICBT is an efficacious treatment for SAD. Thus, one can claim with a high degree of certainty that ICBT leads to a large reduction of social anxiety as well as to improvements regarding depressive symptoms, general anxiety and quality of life. The randomised design of Study I makes it possible to draw the conclusion that the demonstrated improvements were caused by the treatment and would not have occurred in the absence of it. Taken together with the results from other RCTs investigating the efficacy of ICBT for SAD, conducted by independent research groups, the evidence supporting the treatment is massive [13, 14, 208-211, 215-217, 260].

However, the mechanisms of the treatment are less well understood. In Study I, the results only partially supported our hypothesis that ICBT would be superior to unguided bibliotherapy. As a matter of fact, as the bibliotherapy group made moderate to large improvements, neither the online features nor the therapist contact seem necessary to produce treatment gains. This suggests that the content of the treatment is important, i.e. the self-help texts which on which the treatment heavily relies.

As bibliotherapy performed relative well on measures of social anxiety, it is warranted to ask whether the online features, which require therapist time to operate and substantial costs to develop, are redundant. The answer to that question depends on perspective. First, the scientific evidence supporting bibliotherapy for SAD is much more limited. Only four RCTs have been conducted using unassisted self-help and only those conducted by my research group have demonstrated strong effects [185, 186, 210]. For example, on the measures SIAS and SPS, employed across studies, effect sizes ranged between 0.28 and 0.38 (albeit higher if analysing only completers) [185, 210] in the other studies compared to a 0.65-67 effect size range in Study I [186].
Second, although our prediction that ICBT would be superior to bibliotherapy was only partially supported, there was a trend towards stronger effect for ICBT. The average baseline to follow-up effect size on social anxiety measures was 1.40 in the ICBT group compared to 0.86 in the bibliotherapy group.

Assuming effect sizes of the magnitude found in Study I were generally true, bibliotherapy would be a good option under the circumstance that one were willing to pay very little for additional gains compared to no treatment. This would be the case in countries or regions with no or very limited funds to provide other treatments for SAD. Nevertheless, the effect sizes are too small to be sufficient if one has the ambition to

provide a treatment that is as effective as conventional CBT. Further arguments in favour of ICBT rather than bibliotherapy, increasingly relevant to modern psychiatry, are the possibilities to easily and efficiently evaluate and monitor the treatment.

4.1.2 Effectiveness of ICBT for SAD

Effectiveness refers to the degree to which a treatment is feasible and can produce strong effects in real-world clinical situations [205, 206]. Study II of this thesis has demonstrated that ICBT can be at least as effective as cognitive behavioural group therapy (CBGT) when delivered in a psychiatric setting. Thus, ICBT does not only produce large effects when offered in a university context to self-referred patients using primarily self-assessments and telephone interviews, but also within regular health care. Important to bear in mind is that effectiveness not only refers to the characteristics of the patients. Indeed, Titov and co-workers found that although a sample from an outpatient clinic had more social anxiety according to the SPS (but not on the SIAS) and were more likely to be single compared to Internet clinic patients, on most variables the two patient groups were similar [261].

This means that the effectiveness strengths of Study II lie mainly elsewhere. One of the most important is that the general rule was that patients were assessed and treated by psychiatrists and psychologists working as clinicians and not researchers. This is an important aspect as it means that ICBT proved to be effective and feasible even when delivered under regular care reinforcement contingencies. That is, the persons involved carried out their work as part of clinical routing practice, and thus were not unusually highly motivated by scientific reinforcers. Taken together with the open trial [214] and the recently published Australian RCT [207] conducted in a psychiatric outpatient setting, the conclusion is that ICBT for SAD is an effective treatment. Another strong indication of the treatment's effectiveness is that all accumulated evidence contains no conflicting results. That is, the work by Titov and co-workers in Australia and by Berger and colleagues in Switzerland together with the studies by my research group, under the supervision of Andersson and Lindefors, all indicate that ICBT for SAD is effective. This is displayed in Table 6 below presenting main results from all published RCTs in the field.

A limitation of study II in terms of effectiveness is that participants were randomised to the treatment arms. This is unrealistic to happen in clinical routine practice and the only way to get around this problem of external validity is to deliver the treatment outside the context of a research study and evaluate the treatment as part of regular care. Partially as a consequence of the findings presented in this thesis, the ICBT for SAD described herein is now available at the Internet Psychiatry Clinic in Stockholm, Sweden (www.internetpsykiatri.se) within the context of regular psychiatric health care. More than 200 patients with SAD have received treatment and preliminary analyses indicate that the treatment yields large to moderate effect sizes. Considering the nature of ICBT, it is theoretically plausible that it would transfer well to a clinical setting. In conventional psychological treatment, therapist drift refers to the tendency of therapists to divert from the protocol when delivering treatment in clinical settings [262]. Because of the firm structure of ICBT, e.g. fixed modules and homework assignments, this is unlikely to occur. In conclusion, empirical evidence as well as

theoretical arguments suggest that ICBT for SAD is an effective treatment also when delivered in regular health care.

Table 6. Overview of RCTs investigating the effect of ICBT for SAD

Country [reference]	Treatment arms	N	Outcome measure	Main results	Effect size *d* of active treatment (Pre-Post) (note: arms as denoted in second column)	Setting	Year
Sweden [13]	a. ICBT + exposure b. WLC	64	LSAS-SR	ICBT superior to WLC	a. 0.91	University, Self-referral only	2006
Sweden [14]	a. ICBT + tel. support b. WLC	60	LSAS-SR	ICBT superior to WLC	a.1.00	University, Self-referral only	2007
Sweden [209]	a. ICBT + exposure b. ICBT	38	LSAS-SR	Over-lapping CIs of TXs	a. 0.82 b. 1.01	University, Self-referral only	2008
Sweden [Study I]	a. ICBT b. BIB c. WLC	120	LSAS-SR	ICBT and BIB superior to WLC, ICBT partially superior to BIB	a. 0.93 b. 0.78	University, Self-referral only	2009
Sweden [186]	a. ICBT b. BIB c. BIB + DG d. IAR	115	LSAS-SR	Superiority not established	a. 1.35 b. 0.71 c. 1.42 d. 0.99	University, Self-referral only	2009
Sweden [Study II]	a. ICBT b. CBGT	126	LSAS	ICBT at least as effective as CBGT	a. 1.42 b. 0.97	Outpatient clinic, referral and self-referral	2011
Australia [211]	a. ICBT b. WLC	105	SIAS, SPS	ICBT superior to WLC	a. 1.24 (SIAS) a. 1.06 (SPS)	University, Self-referral only	2008
Australia [212]	a. ICBT b. WLC	88	SIAS, SPS	ICBT superior to WLC	a. 1.21 (SIAS) a. 1.14 (SPS)	University, Self-referral only	2008
Australia [210]	a. ICBT b. Unguided ICBT c. WLC	98	SIAS, SPS	ICBT superior to Unguided ICBT and WLC, Unguided ICBT not superior to WLC	a.1.47 (SIAS) and 1.17 (SPS); b. 0.36 (SIAS) and 0.28 (SPS)	University, Self-referral only	2008
Australia [213]	a. Unguided ICBT b. Unguided ICBT + tel. reminders	168	SIAS, SPS	Unguided ICBT + tel. reminders superior to unguided ICBT	a. 1.41 (SIAS) and 0.89 (SPS); b. 0.98 (SIAS) and 0. 73 (SPS)	University, Self-referral only	2009
Australia [208]	a. ICBT + technician aid b. ICBT with guided DG	85	SIAS, SPS	ICBT+ technician aid equivalent to ICBT + guided DG	a. 1.47 (SIAS) and 1.15 (SPS) b. 1.56 (SIAS) and 1.15 (SPS)	University, Self-referral only	2009
Australia [215]	a. ICBT b. ICBT + motivational support	113	SIAS, SPS	ICBT + enhancement not superior to ICBT	a. 1.16 (SIAS) and 1.04 (SPS); b. 1.15 (SIAS) and 0.75 (SPS)	University, Self-referral only	2010
Australia [207]	a. ICBT b. Group CBT	37	SIAS, SPS	Superiority not established	a. 0.74 (SIAS) and 0.58 (SPS) b. 0.89 (SIAS) and 0.82 (SPS)*	Outpatient Anxiety Disorders Clinic, GP referral	2011
Switzerland [216]	a. ICBT b. WLC	52	LSAS-SR	ICBT superior to WLC	a. 0.82	University, Self-referral	2009
Switzerland [217]	a. ICBT b. U-ICBT c. Flexible supported ICBT	81	LSAS-SR	Superiority not established	a. 1.53 b. 1.48 c. 1.41	University, Self-referral	2011

*=Calculated by thesis author (not in paper); Abbreviations: ICBT, Internet-based Cognitive Behaviour Therapy; BIB, Bibliotherapy; WLC, Waiting list control; TX, Treatment; U-ICBT, Unguided ICBT; DG, Discussion group; Tel., telephone; LSAS-SR, Liebowitz Social Anxiety Scale-self report; SIAS, Social Interaction Scale; SPS, Social Phobia Scale. Note: study by Botella et al. [260] not included in the table as it was restricted to fear of public speaking.

4.1.3 Long-term effect of ICBT for SAD

An important aspect of ICBT for SAD is whether the effects are enduring. As the results from Study III showed, the course of improvement seems to be that participants are moderately improved immediately after therapy and make further improvements within the following year. These effects are in turn enduring over at least five years. These results extend the previous research on ICBT for SAD using a shorter follow-up period [238]. Interestingly, the effects demonstrated in Study III are in line with those of the only five-year follow-up trial of conventional CBT for SAD I have found [235].

It is quite remarkable that a treatment over nine weeks can yield such long-lasting effects, and of course a natural objection to the claim of long-term effectiveness is the uncertainty regarding cause and effect. For ethical reasons, it is highly doubtful to use waiting list or placebo controls that do not receive the active treatment for this long period of time. However, a study that came close to using a placebo group at five-year follow-up was the one by Heimberg and co-workers in which CBGT was compared to supportive group psychotherapy [235]. Although attrition rates were substantial, CBGT participants remained more improved than group psychotherapy participants at five-year follow-up.

As for Study III, what can be done is to make a theoretical estimate of the mechanisms of CBT and of what might have happened to participants in the control group had they received no treatment. In a study by Yonkers and co-workers, it was found that over a five-year period, the cumulative probability of achieving a full remission from SAD was 29% in men and 32% in women [69]. In comparison, 64% (51) of the participants in Study III were classified as very much or much improved at five-year follow-up, suggesting an additional effect of the treatment in relation to the natural course of SAD. Furthermore, as one of the most important proposed mechanisms of CBT for SAD is reduced anxiety by repeated exposure, it is theoretically predicted that gains are maintained as CBT stresses the importance of making long-term behaviour change [22]. As evidence in this field shows that results from efficacy studies can be generalised to clinical settings, it is fair to conclude that ICBT for SAD can be effective over half a decade.

4.1.4 Cost-effectiveness and cost-utility of ICBT for SAD

Study IV demonstrated that ICBT for SAD can be cost-effective compared to CBGT when taking a societal perspective. Intriguingly, the most likely outcome according to the economic evaluation was that ICBT yields incremental effects to a lower cost, thus being cost-effective compared to CBGT regardless of willingness to pay. As this is the only trial so far using a randomised control over potential confounders, it is a bit too early to claim strong evidence for cost-effectiveness of ICBT for SAD. However, results from a trial by Titov and co-workers using a different design is in line with the findings of Study IV [204].

As would be expected from the concept of SAD from a CBT perspective, the reduced costs following treatment was in the realm of indirect non-medical costs i.e. loss of productivity. This suggests that the same components of treatment leading to reduced

social anxiety also cause patients to engage more in work related activities. The cost analysis showed that although the interventions introduced some costs of their own, these costs were offset by increased productivity levels within one year.

Were the results of Study IV to hold, the decision to choose between ICBT and CBGT for SAD is relatively straightforward from a health care perspective. From a societal perspective, however, the preference of one treatment over the other is not as obvious. Assuming that both treatments yield about the same effects and are long-term effective, the relative cost-effectiveness of ICBT would likely diminish over time. This is because both treatments displayed the same effects in terms of cost reductions and the net cost benefit of ICBT was due to lower costs of treatment. Thus, with time the cost difference between treatments will be negligible compared to the societal economic gains that both treatments produce. In conclusion, in the shorter term ICBT is cost-effective compared to CBGT from a health care and societal perspective. In the longer run, society might make fairly equal economic gains by increasing availability to either of the treatments.

4.1.5 Determinants of treatment outcome of ICBT and cognitive behavioural group therapy for SAD

The results from study V showed that patient demographics (having children, working full time), clinical characteristics (less depressive symptoms) as well as therapy process related measures (treatment adherence, higher expectation of treatment effectiveness) predicted better outcome of ICBT and CBGT for SAD. These factors were stable across different methods of measuring outcome. Overall, the hypothesis that stronger social support would be associated with better outcome was corroborated, potentially mediated through better opportunities to find suitable exposure situations. None of the investigated candidate genes had a significant predictive or moderating effect.

As for moderators, general anxiety, and to a lesser extent, comorbid depression and personality traits of impulsivity were found to interact with treatment type on outcome. The picture that emerges is that ICBT tend to have incremental effects for persons with lower levels of general anxiety and depressive symptoms while CBGT could be more suitable for persons with "need for change and action" [252] and who are less inclined to plan activities thoroughly.

These findings seem reasonable in that the full benefits of ICBT, e.g. the freedom to plan one's own treatment and the possibility of going through treatment stages in an individualised pace, are probably best reaped if the overall level of psychiatric symptoms is somewhat lower. Furthermore, it makes sense that the advantages of CBGT, e.g. firm structure, clear cues for treatment actions including built-in exposure possibilities, are best capitalised upon if one is more spontaneous and non-planning.

Computer skills did not moderate treatment effects. Taken together with the finding that higher age predicted absence of SAD diagnosis, this refutes the notion that ICBT is for younger people with special interest in computers.

These results have several theoretical and clinical implications. From a theoretical view, the predictors found in this study might be used as an empirical ground from which hypotheses of treatment interventions can be generated and tested. One could design experiments to test whether the total proportion of participants responding to treatment would increase if classifying participants a priori and randomising them to standard ICBT or augmented treatment. For example, younger patients with higher levels of depressive symptoms might benefit from a treatment with added social support. Regarding the null findings of genetic factors, the results suggest that the effects of these variables are fairly small and potentially complex.

As stated above, the results of Study V has important clinical implications. These will be discussed below under the Clinical implications section taking all studies in the thesis into consideration. But first a few words on the most central methodological limitations of this thesis.

4.2 METHODOLOGICAL LIMITATIONS

I view the following limitations of the studies in this thesis as most essential. In none of the RCTs described here a credible placebo condition was used. This means that the specific mechanisms of the treatment remain unknown. As for Study II and III comparing two active treatments, the same limitation makes it possible to claim that the improvements would have occurred in the absence of treatment. Considering the chronicity of SAD [263], this is however very unlikely (participants in study II, IV an V had had suffered from SAD for 21 years on average). Second, all studies used inclusion criteria which might have imposed restriction of the samples compared to clinical settings, e.g. in terms of risk of suicidal behaviours. However, the aim was to use inclusion criteria that would resemble the ones used in clinical practice which meant allowing for psychiatric comorbidity.

4.3 CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

The findings of this thesis are of clear clinical value. The main implication is that ICBT for SAD is ready for implementation and dissemination within a regular health care context. It is safe to say that the scientific evidence supporting the effectiveness and the safety of the treatment is substantial and of high quality. The Swedish Council on Health Technology assessment (SBU), the governmental agency that evaluates health care interventions, assesses the empirical support of treatments on a 4-point scale. According to this scale, a treatment can be considered having highest possible empirical support if its effect has been demonstrated in at least two high quality RCTs conducted by independent research groups without conflicting evidence [264]. These criteria are by far fulfilled when it comes to ICBT for SAD.

When adding the findings regarding long-term effects and cost-effectiveness of ICBT, the advantages of this treatment are striking. As stated in the introduction section, CBT

is available to only a few for several reasons, not at least due to a lack of trained therapists. ICBT is probably the most promising way of increasing accessibility to CBT on a large scale. Not only can it be used as general mean of increasing the number of patients treated by each psychologist, it can in fact be the only realistic way of increasing accessibility in remote rural areas.

Although effect sizes of ICBT for SAD may be in parity with those of conventional CBT, it is important to remember that about a third of patients receiving ICBT in Studies I-II were not clinically significant improved. One of the most central roles that ICBT can play in future psychiatric care is to constitute the first step of treatment, thereby setting free resources to provide treatment of more intensified and complex nature for those who do not respond to ICBT. This could be a new way of using resources more efficiently and thus increasing the overall proportion of patients that achieves remission from SAD. This would be a pivotal shift from psychiatry of today which so often is referred to as binary – either you get it all (i.e. the full conventional CBT) or nothing. In essence, ICBT ought to be a complement to conventional CBT, not a substitute.

An important question is whether all patients should be offered ICBT. As demonstrated in Study V, treatment outcome varies depending on several demographic and clinical variables. In addition, some symptom profiles moderate the effect of ICBT and conventional CBT for SAD. This suggests that on a fairly early treatment stage, patients at high risk of non-responding could be identified. Instead of letting everyone go through ICBT in the standard fashion knowing that a substantial proportion will be treatment failures, an interesting alternative would be to differentiate treatment interventions based on these predictor variables.

This does not mean that young, single patients with high levels of depressive symptoms and general anxiety automatically should be discouraged to be treated with ICBT. However, it might be of especially high clinical value to monitor these patients with additional carefulness and to have an alternative treatment plan ready to be implemented at an early stage. This could be face-to-face sessions with the same therapist as one is treated by online, pharmacological treatment with SSRIs, or perhaps in a near future, the combination of the extinction enhancing drug D-cycloserine and in-session exposure.

So, how does one actually implement ICBT for SAD within regular psychiatric care? As mentioned, the Internet Psychiatry Clinic in Stockholm operates as a regular unit within psychiatric health care. Today, persons with SAD are eligible to seek treatment although the clinic initially offered treatment for panic disorder and depression only. Several lessons are learned from this experience.

First, as ICBT requires specific skills in terms of CBT competence, computer programming and diagnostic procedures, it should constitute a separate unit of psychologists and psychiatrists rather than being implemented as a treatment package in a general practitioner's context. Although research has shown that many parts of the regular treatment procedure itself can be handled by less skilled personnel [208], it is of utmost importance that experienced and CBT trained psychologists are responsible for

the treatment. This is because complex cases need skilled supervision and that, in order to refine and develop the treatment, one has to have a profound understanding of its mechanisms, theoretically as well as practically.

One other important aspect is high quality of diagnostic procedures. Because of the firm structure of the treatment, the therapist's possibilities to adjust the treatment content in case of discovering that the patient has been misclassified diagnostically are limited (e.g. if it turns out that the patient has panic disorder rather than SAD). Thus, compared to regular outpatient psychiatric care, it is even more important that personnel conducting diagnostic assessments are highly competent in this regard.

Finally, in order to truly serve the purpose of increasing availability to CBT, an important lessoned learned is to allow self-referral and not restrict ICBT to those referred from other health care providers. If adhering to these principles, it is my conviction that in the near future ICBT will be an indispensible part of regular psychiatric health care in the treatment of SAD.

4.4 CONCLUSIONS

This thesis has demonstrated that ICBT for SAD is efficacious, effective in a clinical setting, and cost-effective. Furthermore, the studies presented here have shown that it is possible to predict outcome of ICBT, and that ICBT yields improvements that are long-term enduring. As I see it, this treatment is the most promising mean for making CBT available for the many persons affected by SAD who presently lack access to it. ICBT for SAD is ready for implementation and dissemination.

5 ACKNOWLEDGEMENTS

Of course, the studies described in this thesis are by no means the result of a single man's work. I would like to give my warmest thanks to the following persons without whose efforts this thesis would have remained just an interesting phenomenon in the world of ideas.

First of all, my main supervisor **Nils Lindefors** and co-supervisors **Gerhard Andersson** and **Christian Rück** have been invaluable in all stages of my doctoral studies: encouraging and supportive in times of struggle as well as constituting a Superego imposing sound restraints in times of slightly exaggerated optimism. And naturally, constant providers of golden drops of wisdom.

As for the harsh realities of conducting research as a PhD-student, without my constant brother in hope and despair, wonderful friend and always available free-of-charge therapist **Brjánn Ljótsson**, this journey would have come closer to a Golgotha walk instead of the gentler and inspiring Iron-man Triathlon it actually was.

My warmest gratitude also goes to great friend and colleague **Erik Andersson** (a.k.a. Mr Bootstrap, a.k.a. The Hair) for all the therapy conducted, and the important advice on health economics and bikram yoga. I feel the same gratitude towards **Monica Hellberg** for impressive relentlessness in data collection, how you did it with maintained mental and somatic health remains a mystery. And of course, **Marita Signarsson**, the rock solid administrative foundation on which this thesis rests, deserves all the credit possible. My deep appreciation also goes to **Ewa Mörtberg**, my mentor and great CBT advisor.

At Unit M46 of the Karolinska University Hospital Huddinge, the world's greatest colleagues (p<.001) have gilded all those grey Monday mornings and made lunch discussions the indispensable highlight of the workday. The following have made vital contributions to this thesis and have all my gratitude: **Sara Rydh,** therapist and the heroine saviour of the thesis application; **Anna-Clara Hellstadius**, therapist and merciless quality controller of all treatments conducted; **Kerstin Blom**, therapist and Karaoke queen; **Karin Hyland**, psychiatrist and Tea-Kwondo black-belt; Lieutenant **Carl Granfors**, psychiatrist and guarantor of good hope and high morals in all situations; **Anne-Christine Fredman**, psychiatrist with the greatest hospitality in Tullinge; **Diana Radu Djurfeldt,** the most positive and energetic psychiatrist north of the Dunărea; and **Sergej Andréewitch** psychiatrist and downhill professional.

More collegial heroes from the M46 Unit are **Lisa Jansson**, my cicerone in the truly important domains in life such as LEAN production and etology; **Karin Larse**, secretary whose kindness is surpassed only by her efficiency; **Evelyn Andersson,** expert in haplotypes and Norwegian foods; **Katja Hatwig,** saviour of my clinical life by always covering for me on my endless research sabbaticals; **Gurli Engström,** the light of the clinic; **Lisa Falk**, therapist and just great in all ways; **Anna Hägg**, stoic endurer of all my difficulties in properly handling the patient booking system; head of the unit **Peter Eriksson**, enabler of my combined work as a PhD-student and as a clinical psychologist (and this with a smile); **Jan Bergström,** therapist showing that going to Paris might actually be the best thing to do when in doubt; **Viktor Kaldo**, one

6 REFERENCES

1.	Burton R. *The anatomy of melancholy: What it is, with all the kindes, causes, symptomes, prognosticks, and severall cures of it: In three maine partitions, with their seuerall sections, members, and subsections, philosophically, medicinally, historically opened and cut up.* 1932 ed. Jackson H, editor. New York: New York Review of Books; 1624; 2001.
2.	American Psychiatric Association. Task Force on Nomenclature and Statistics., Committee on Nomenclature and Statistics. *Diagnostic and statistical manual of mental disorders.* 3d ed. Washington, D.C.: American Psychiatric Association; 1980.
3.	Magee WJ, Eaton WW, Wittchen HU, McGonagle KA, Kessler RC. Agoraphobia, simple phobia, and social phobia in the national comorbidity survey. *Arch Gen Psychiatry* 1996; 53: 159-68.
4.	Wittchen HU, Fuetsch M, Sonntag H, Müller N, Liebowitz M. Disability and quality of life in pure and comorbid social phobia. Findings from a controlled study. *Eur Psychiatry* 2000; 15: 46-58.
5.	Kessler RC, Stein MB, Berglund P. Social phobia subtypes in the national comorbidity survey. *Am J Psychiatry* 1998; 155: 613-9.
6.	Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Arch Gen Psychiatry* 2005; 62: 593-602.
7.	Chartier MJ, Hazen AL, Stein MB. Lifetime patterns of social phobia: A retrospective study of the course of social phobia in a nonclinical population. *Depress Anxiety* 1998; 7: 113-21.
8.	Furmark T, Tillfors M, Everz P, Marteinsdottir I, Gefvert O, Fredrikson M. Social phobia in the general population: Prevalence and sociodemographic profile. *Soc Psychiatry Psychiatr Epidemiol* 1999; 34: 416-24.
9.	Heimberg RG, Dodge CS, Hope DA, Kennedy CR, Zollo LJ, Becker RE. Cognitive behavioral group treatment for social phobia: Comparison with a credible placebo control. *Cognitive Ther Res* 1990; 14: 1-23.
10.	Jorstad-Stein EC, Heimberg RG. Social phobia: An update on treatment. *Psychiatr Clin North Am* 2009; 32: 641-63.
11.	Shapiro DA, Cavanagh K, Lomas H. Geographic inequity in the availability of cognitive behavioural therapy in England and Wales. *Behav Cogn Psychother* 2003; 31: 185-92.
12.	Andersson G. Using the internet to provide cognitive behaviour therapy. *Behav Res Ther* 2009; 47: 175-80.
13.	Andersson G, Carlbring P, Holmström A, Sparthan E, Furmark T, Nilsson-Ihrfelt E, Buhrman M, Ekselius L. Internet-based self-help with therapist feedback and in vivo group exposure for social phobia: A randomized controlled trial. *J Consult Clin Psychol* 2006; 74: 677-86.
14.	Carlbring P, Gunnarsdottir M, Hedensjo L, Andersson G, Ekselius L, Furmark T. Treatment of social phobia: Randomised trial of internet-delivered cognitive-behavioural therapy with telephone support. *Br J Psychiatry* 2007; 190: 123-8.
15.	American Psychiatric Association., Task Force on DSM-IV. *Diagnostic and statistical manual of mental disorders: DSM-IV.* 4th ed. Washington, DC: American Psychiatric Association; 1994.
16.	American Psychiatric Association. Arlington, Va.2011 [2011]; Available from: http://www.psych.org/mainmenu/research/dsmiv.aspx.
17.	World Health Organization. 2011 [2011]; Available from: http://www.who.int/classifications/icd/en/.

18. Bertelsen A. Reflections on the clinical utility of the ICD-10 and DSM-IV classifications and their diagnostic criteria. *Aust N Z J Psychiatry* 1999; 33: 166-73.

19. World Health Organization. The international conference for the tenth revision of the international classification of diseases. Strengthening of epidemiological and statistical services unit. World health organization, geneva. *World Health Stat Q* 1990; 43: 204-45.

20. Sorensen MJ, Mors O, Thomsen PH. DSM-IV or ICD-10-dcr diagnoses in child and adolescent psychiatry: Does it matter? *Eur Child Adolesc Psychiatry* 2005; 14: 335-40.

21. Andrews G, Slade T, Peters L. Classification in psychiatry: ICD-10 versus DSM-IV. *Br J Psychiatry* 1999; 174: 3-5.

22. Heimberg RG, Becker RE. *Cognitive-behavioral group therapy for social phobia. Basic mechanisms and clinical strategies.* New York: Guilford Press; 2002.

23. American Psychiatric Association., Work Group to Revise DSM-III. *Diagnostic and statistical manual of mental disorders : DSM-III-r.* 3rd ed. Washington, DC: American Psychiatric Association; 1987.

24. Liebowitz MR, Heimberg RG, Fresco DM, Travers J, Stein MB. Social phobia or social anxiety disorder: What's in a name? *Arch Gen Psychiatry* 2000; 57: 191-2.

25. Barlow DH. *Clinical handbook of psychological disorders: A step-by-step treatment manual.* 3rd ed. New York: Guilford Press; 2001.

26. Heimberg RG, Hope DA, Dodge CS, Becker RE. DSM-III-r subtypes of social phobia. Comparison of generalized social phobics and public speaking phobics. *J Nerv Ment Dis* 1990; 178: 172-9.

27. Stein MB, Chavira DA. Subtypes of social phobia and comorbidity with depression and other anxiety disorders. *J Affect Disord* 1998; 50 Suppl 1: S11-6.

28. Widiger TA. Generalized social phobia versus avoidant personality disorder: A commentary on three studies. *J Abnorm Psychol* 1992; 101: 340-3.

29. American Psychiatric Association. *Diagnostic criteria from DSM-IV-tr.* Washington, D.C.: American Psychiatric Association; 2000.

30. Reich J. The relationship of social phobia to avoidant personality disorder: A proposal to reclassify avoidant personality disorder based on clinical empirical findings. *Eur Psychiatry* 2000; 15: 151-9.

31. Reich J, Noyes R, Jr., Yates W. Alprazolam treatment of avoidant personality traits in social phobic patients. *J Clin Psychiatry* 1989; 50: 91-5.

32. Liebowitz MR, Schneier F, Campeas R, Hollander E, Hatterer J, Fyer A, Gorman J, Papp L, Davies S, Gully R, et al. Phenelzine vs atenolol in social phobia. A placebo-controlled comparison. *Arch Gen Psychiatry* 1992; 49: 290-300.

33. Brown EJ, Heimberg RG, Juster HR. Social phobia subtype and avoidant personality disorder: Effect on severity of social phobia, impairment, and outcome of cognitive behavioral treatment. *Behav Ther* 1995; 26: 467-86.

34. Hofmann SG, Newman MG, Becker E, Taylor CB, Roth WT. Social phobia with and without avoidant personality disorder: Preliminary behavior therapy outcome findings. *J Anxiety Disord* 1995; 9: 427-38.

35. Ruscio AM, Brown TA, Chiu WT, Sareen J, Stein MB, Kessler RC. Social fears and social phobia in the USA: Results from the national comorbidity survey replication. *Psychol Med* 2008; 38: 15-28.

36. Furmark T. Social phobia: Overview of community surveys. *Acta Psychiatr Scand* 2002; 105: 84-93.

37. Faravelli C, Zucchi T, Viviani B, Salmoria R, Perone A, Paionni A, Scarpato A, Vigliaturo D, Rosi S, D'Adamo D, Bartolozzi D, Cecchi C, Abrardi L. Epidemiology of social phobia: A clinical approach. *Eur Psychiatry* 2000; 15: 17-24.

38. Heimberg RG. Cognitive-behavioral therapy for social anxiety disorder: Current status and future directions. *Biol Psychiatry* 2002; 51: 101-8.

39. Nelson EC, Grant JD, Bucholz KK, Glowinski A, Madden PAF, Reich W, Heath AC. Social phobia in a population-based female adolescent twin sample: Co-morbidity and associated suicide-related symptoms. *Psychol Med* 2000; 30: 797-804.

40. Davidson JR, Hughes DL, George LK, Blazer DG. The epidemiology of social phobia: Findings from the duke epidemiological catchment area study. *Psychol Med* 1993; 23: 709-18.

41. DeWit DJ, Ogborne A, Offord DR, MacDonald K. Antecedents of the risk of recovery from DSM-III-r social phobia. *Psychol Med* 1999; 29: 569-82.

42. Lieb R, Isensee B, von Sydow K, Wittchen HU. The early developmental stages of psychopathology study (edsp): A methodological update. *Eur Addict Res* 2000; 6: 170-82.

43. Wittchen HU, Fehm L. Epidemiology and natural course of social fears and social phobia. *Acta Psychiatr Scand Suppl* 2003: 4-18.

44. Beesdo K, Bittner A, Pine DS, Stein MB, Hofler M, Lieb R, Wittchen HU. Incidence of social anxiety disorder and the consistent risk for secondary depression in the first three decades of life. *Arch Gen Psychiatry* 2007; 64: 903-12.

45. Stein MB. An epidemiologic perspective on social anxiety disorder. *J Clin Psychiatry* 2006; 67 Suppl 12: 3-8.

46. Fehm L, Pelissolo A, Furmark T, Wittchen H-U. Size and burden of social phobia in europe. *Eur Neuropsychopharmacol* 2005; 15: 453-62.

47. Lampe L, Slade T, Issakidis C, Andrews G. Social phobia in the Australian national survey of mental health and well-being (nsmhwb). *Psychol Med* 2003; 33: 637-46.

48. Bruch MA, Fallon M, Heimberg RG. Social phobia and difficulties in occupational adjustment. *Journal of Councelling Psychology* 2003.

49. Dahl AA, Dahl CF. Are there gender differences in impairment associated with high social anxiety? A community-based study. *J Anxiety Disord* 2010; 24: 487-93.

50. Olatunji BO, Cisler JM, Tolin DF. Quality of life in the anxiety disorders: A meta-analytic review. *Clin Psychol Rev* 2007; 27: 572-81.

51. Buckner JD, Timpano KR, Zvolensky MJ, Sachs-Ericsson N, Schmidt NB. Implications of comorbid alcohol dependence among individuals with social anxiety disorder. *Depress Anxiety* 2008; 25: 1028-37.

52. Zimmermann P, Wittchen HU, Hofler M, Pfister H, Kessler RC, Lieb R. Primary anxiety disorders and the development of subsequent alcohol use disorders: A 4-year community study of adolescents and young adults. *Psychol Med* 2003; 33: 1211-22.

53. Schneier FR, Johnson J, Hornig CD, Liebowitz MR, Weissman MM. Social phobia. Comorbidity and morbidity in an epidemiologic sample. *Arch Gen Psychiatry* 1992; 49: 282-8.

54. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-r psychiatric disorders in the United States. Results from the national comorbidity survey. *Arch Gen Psychiatry* 1994; 51: 8-19.

55. Stein MB, Walker JR, Forde DR. Setting diagnostic thresholds for social phobia: Considerations from a community survey of social anxiety. *Am J Psychiatry* 1994; 151: 408-12.

56. Vega WA, Kolody B, Aguilar-Gaxiola S, Alderete E, Catalano R, Caraveo-Anduaga J. Lifetime prevalence of DSM-III-r psychiatric disorders among urban and rural mexican americans in California. *Arch Gen Psychiatry* 1998; 55: 771-8.

57. Slade T, Johnston A, Oakley Browne MA, Andrews G, Whiteford H. 2007 national survey of mental health and wellbeing: Methods and key findings. *Aust N Z J Psychiatry* 2009; 43: 594-605.

58. Andrews G, Henderson S, Hall W. Prevalence, comorbidity, disability and service utilisation. Overview of the Australian national mental health survey. *Br J Psychiatry* 2001; 178: 145-53.

59. Offord DR, Boyle MH, Campbell D, Goering P, Lin E, Wong M, Racine YA. One-year prevalence of psychiatric disorder in ontarians 15 to 64 years of age. *Can J Psychiatry* 1996; 41: 559-63.

60. Pelissolo A, Andre C, Moutard-Martin F, Wittchen HU, Lepine JP. Social phobia in the community: Relationship between diagnostic threshold and prevalence. *Eur Psychiatry* 2000; 15: 25-8.

61. Lepine JP, Lellouch J. Classification and epidemiology of social phobia. *Eur Arch Psychiatry Clin Neurosci* 1995; 244: 290-6.

62. Bijl RV, Ravelli A, van Zessen G. Prevalence of psychiatric disorder in the general population: Results of the Netherlands mental health survey and incidence study (nemesis). *Soc Psychiatry Psychiatr Epidemiol* 1998; 33: 587-95.

63. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. *Arch Gen Psychiatry* 2005; 62: 617-27.

64. Kessler RC, Stang P, Wittchen HU, Stein M, Walters EE. Lifetime co-morbidities between social phobia and mood disorders in the US national comorbidity survey. *Psychol Med* 1999; 29: 555-67.

65. Chartier MJ, Walker JR, Stein MB. Considering comorbidity in social phobia. *Soc Psychiatry Psychiatr Epidemiol* 2003; 38: 728-34.

66. Wittchen HU, Stein MB, Kessler RC. Social fears and social phobia in a community sample of adolescents and young adults: Prevalence, risk factors and co-morbidity. *Psychol Med* 1999; 29: 309-23.

67. Tillfors M, Furmark T, Ekselius L, Fredrikson M. Social phobia and avoidant personality disorder: One spectrum disorder? *Nord J Psychiatry* 2004; 58: 147-52.

68. Schneier FR, Foose TE, Hasin DS, Heimberg RG, Liu SM, Grant BF, Blanco C. Social anxiety disorder and alcohol use disorder co-morbidity in the national epidemiologic survey on alcohol and related conditions. *Psychol Med* 2010; 40: 977-88.

69. Yonkers KA, Dyck IR, Keller MB. An eight-year longitudinal comparison of clinical course and characteristics of social phobia among men and women. *Psychiatr Serv* 2001; 52: 637-43.

70. Acarturk C, Smit F, de Graaf R, van Straten A, Ten Have M, Cuijpers P. Economic costs of social phobia: A population-based study. *J Affect Disord* 2009; 115: 421-9.

71. Patel A, Knapp M, Henderson J, Baldwin D. The economic consequences of social phobia. *J Affect Disord* 2002; 68: 221-33.

72. Lim D, Sanderson K, Andrews G. Lost productivity among full-time workers with mental disorders. *The Journal of Mental Health Policy and Economics* 2000; 3: 139-46.

73. Ollendick TH, Hirshfeld-Becker DR. The developmental psychopathology of social anxiety disorder. *Biol Psychiatry* 2002; 51: 44-58.

74. Kendler KS, Karkowski LM, Prescott CA. Fears and phobias: Reliability and heritability. *Psychol Med* 1999; 29: 539-53.

75. Hettema JM, Neale MC, Myers JM, Prescott CA, Kendler KS. A population-based twin study of the relationship between neuroticism and internalizing disorders. *Am J Psychiatry* 2006; 163: 857-64.

76. Kendler KS, Myers J, Prescott CA, Neale MC. The genetic epidemiology of irrational fears and phobias in men. *Arch Gen Psychiatry* 2001; 58: 257-65.

77. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. The genetic epidemiology of phobias in women. The interrelationship of agoraphobia, social phobia, situational phobia, and simple phobia. *Arch Gen Psychiatry* 1992; 49: 273-81.

78. Stein MB, Jang KL, Livesley WJ. Heritability of social anxiety-related concerns and personality characteristics: A twin study. *J Nerv Ment Dis* 2002; 190: 219-24.

79. Serretti A, Calati R, Mandelli L, De Ronchi D. Serotonin transporter gene variants and behavior: A comprehensive review. *Curr Drug Targets* 2006; 7: 1659-69.

80. Furmark T. Neurobiological aspects of social anxiety disorder. *Isr J Psychiatry Relat Sci* 2009; 46: 5-12.
81. Stein MB, Seedat S, Gelernter J. Serotonin transporter gene promoter polymorphism predicts SSRI response in generalized social anxiety disorder. *Psychopharmacology (Berl)* 2006; 187: 68-72.
82. Smolka MN, Schumann G, Wrase J, Grusser SM, Flor H, Mann K, Braus DF, Goldman D, Buchel C, Heinz A. Catechol-o-methyltransferase val158met genotype affects processing of emotional stimuli in the amygdala and prefrontal cortex. *J Neurosci* 2005; 25: 836-42.
83. Kagan J, Reznick JS, Snidman N. Biological bases of childhood shyness. *Science* 1988; 240: 167-71.
84. Burger JM. *Personality.* 3rd ed. Pacific Grove, Calif.: Brooks/Cole Pub. Co.; 1993.
85. Kagan J, Snidman N. Temperamental factors in human development. *Am Psychol* 1991; 46: 856-62.
86. Hirshfeld-Becker DR, Biederman J, Henin A, Faraone SV, Davis S, Harrington K, Rosenbaum JF. Behavioral inhibition in preschool children at risk is a specific predictor of middle childhood social anxiety: A five-year follow-up. *J Dev Behav Pediatr* 2007; 28: 225-33.
87. Chronis-Tuscano A, Degnan KA, Pine DS, Perez-Edgar K, Henderson HA, Diaz Y, Raggi VL, Fox NA. Stable early maternal report of behavioral inhibition predicts lifetime social anxiety disorder in adolescence. *J Am Acad Child Adolesc Psychiatry* 2009; 48: 928-35.
88. Mick MA, Telch MJ. Social anxiety and history of behavioral inhibition in young adults. *J Anxiety Disord* 1998; 12: 1-20.
89. Schwartz CE, Snidman N, Kagan J. Adolescent social anxiety as an outcome of inhibited temperament in childhood. *J Am Acad Child Adolesc Psychiatry* 1999; 38: 1008-15.
90. Curran JP. Skills training as an approach to the treatment of heterosexual-social anxiety: A review. *Psychol Bull* 1977; 84: 140-57.
91. Levitan MN, Nardi AE. Social skill deficits in socially anxious subjects. *World J Biol Psychiatry* 2009; 10: 702-9.
92. Rapee RM, Lim L. Discrepancy between self- and observer ratings of performance in social phobics. *J Abnorm Psychol* 1992; 101: 728-31.
93. Voncken MJ, Bogels SM. Social performance deficits in social anxiety disorder: Reality during conversation and biased perception during speech. *J Anxiety Disord* 2008; 22: 1384-92.
94. Strahan E, Conger AJ. Social anxiety and its effects on performance and perception. *J Anxiety Disord* 1998; 12: 293-305.
95. Miers AC, Blote AW, Westenberg PM. Peer perceptions of social skills in socially anxious and nonanxious adolescents. *J Abnorm Child Psychol* 2010; 38: 33-41.
96. Inderbitzen-Nolan HM, Anderson ER, Johnson HS. Subjective versus objective behavioral ratings following two analogue tasks: A comparison of socially phobic and non-anxious adolescents. *J Anxiety Disord* 2007; 21: 76-90.
97. Hopko DR, McNeil DW, Zvolensky MJ, Eifert GH. The relation between anxiety and skill in performance-based anxiety disorders: A behavioral formulation of social phobia. *Behav Ther* 2001; 32: 185-207.
98. Rapee RM, Spence SH. The etiology of social phobia: Empirical evidence and an initial model. *Clin Psychol Rev* 2004; 24: 737-67.
99. Shin LM, Liberzon I. The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology* 2010; 35: 169-91.
100. Klumpp H, Angstadt M, Nathan PJ, Phan KL. Amygdala reactivity to faces at varying intensities of threat in generalized social phobia: An event-related functional mri study. *Psychiatry Research: Neuroimaging* 2010; 183: 167-9.
101. Birbaumer N, Grodd W, Diedrich O, Klose U, Erb M, Lotze M, Schneider F, Weiss U, Flor H. Fmri reveals amygdala activation to human faces in social phobics. *Neuroreport* 1998; 9: 1223-6.

102. Evans KC, Wright CI, Wedig MM, Gold AL, Pollack MH, Rauch SL. A functional mri study of amygdala responses to angry schematic faces in social anxiety disorder. *Depress Anxiety* 2008; 25: 496-505.
103. Stein MB, Goldin PR, Sareen J, Zorrilla LT, Brown GG. Increased amygdala activation to angry and contemptuous faces in generalized social phobia. *Arch Gen Psychiatry* 2002; 59: 1027-34.
104. Phan KL, Fitzgerald DA, Nathan PJ, Tancer ME. Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. *Biol Psychiatry* 2006; 59: 424-9.
105. Furmark T, Tillfors M, Marteinsdottir I, Fischer H, Pissiota A, Langstrom B, Fredrikson M. Common changes in cerebral blood flow in patients with social phobia treated with citalopram or cognitive-behavioral therapy. *Arch Gen Psychiatry* 2002; 59: 425-33.
106. Schneier FR, Liebowitz MR, Abi-Dargham A, Zea-Ponce Y, Lin SH, Laruelle M. Low dopamine d(2) receptor binding potential in social phobia. *Am J Psychiatry* 2000; 157: 457-9.
107. Schneier FR, Martinez D, Abi-Dargham A, Zea-Ponce Y, Simpson HB, Liebowitz MR, Laruelle M. Striatal dopamine d(2) receptor availability in OCD with and without comorbid social anxiety disorder: Preliminary findings. *Depress Anxiety* 2008; 25: 1-7.
108. Schneier FR. Pharmacotherapy of social anxiety disorder. *Expert Opin Pharmacother* 2011.
109. Ellis A. *Reason and emotion in psychotherapy.* New York,: L. Stuart; 1962.
110. Dobson KS. *Handbook of cognitive-behavioral therapies.* 2nd ed. New York: Guilford Press; 2001.
111. Hayes SC, Barnes-Holmes D, Roche B. *Relational frame theory: A post-skinnerian account of human language and cognition.* New York: Kluwer Academic/Plenum Publishers; 2001.
112. Clark DM, Wells A. A cognitive model of social phobia. In: Heimberg RG, Leibowitz M, Hope DA, Schneider FR, eds. Social phobia: Diagnosis, assessment and treatment. New York: Guilford press;1995: 63-93.
113. Baldwin JD, Baldwin JI. *Behavior principles in everyday life.* 3rd ed. Upper Saddle River, N.J.: Prentice Hall; 1998.
114. Watson JB, Rayner R. Conditioned emotional reactions. *J Exp Psychol* 1920; 55: 1-14.
115. Öst LG, Hugdahl K. Acquisition of phobias and anxiety response patterns in clinical patients. *Behav Res Ther* 1981; 19: 439-47.
116. Stemberger RT, Turner SM, Beidel DC, Calhoun KS. Social phobia: An analysis of possible developmental factors. *J Abnorm Psychol* 1995; 104: 526-31.
117. Hofmann SG, Ehlers A, Roth WT. Conditioning theory: A model for the etiology of public speaking anxiety? *Behav Res Ther* 1995; 33: 567-71.
118. LeDoux JE. *The emotional brain: The mysterious underpinnings of emotional life.* New York: Simon & Schuster; 1996.
119. Leung AW, Heimberg RG, Holt CS, Bruch MA. Social anxiety and perception of early parenting among American, Chinese American, and social phobic samples. *Anxiety* 1994; 1: 80-9.
120. Hudson JL, Rapee RM. Parent-child interactions in clinically anxious children and their siblings. *J Clin Child Adolesc Psychol* 2002; 31: 548-55.
121. Barrett PM, Rapee RM, Dadds MM, Ryan SM. Family enhancement of cognitive style in anxious and aggressive children. *J Abnorm Child Psychol* 1996; 24: 187-203.
122. Mineka S, Zinbarg R. A contemporary learning theory perspective on the etiology of anxiety disorders: It's not what you thought it was. *Am Psychol* 2006; 61: 10-26.
123. Vriends N, Becker ES, Meyer A, Williams SL, Lutz R, Margraf J. Recovery from social phobia in the community and its predictors: Data from a longitudinal epidemiological study. *J Anxiety Disord* 2007; 21: 320-37.
124. Heinrichs N, Hofmann SG. Information processing in social phobia: A critical review. *Clin Psychol Rev* 2001; 21: 751-70.

125. Clark DM, McManus F. Information processing in social phobia. *Biol Psychiatry* 2002; 51: 92-100.
126. Asmundson GJG, Stein MB. Selective processing of social threat in patients with generalized social phobia: Evaluation using a dot-probe paradigm. *J Anxiety Disord* 1994; 8: 107-17.
127. Amin N, Foa EB, Coles ME. Negative interpretation bias in social phobia. *Behav Res Ther* 1998; 36: 945-57.
128. Rapee RM, Heimberg RG. A cognitive-behavioral model of anxiety in social phobia. *Behav Res Ther* 1997; 35: 741-56.
129. Clark-Carter D. *Doing quantitative psychological research- from design to report.* East Sussex: Psychology Press; 1997.
130. Lieb R, Wittchen HU, Hofler M, Fuetsch M, Stein MB, Merikangas KR. Parental psychopathology, parenting styles, and the risk of social phobia in offspring: A prospective-longitudinal community study. *Arch Gen Psychiatry* 2000; 57: 859-66.
131. Inderbitzen HM, Walters KS, Bukowski AL. The role of social anxiety in adolescent peer relations: Differences among sociometric status groups and rejected subgroups. *J Clin Child Psychol* 1997; 26: 338-48.
132. Gazelle H, Druhen MJ. Anxious solitude and peer exclusion predict social helplessness, upset affect, and vagal regulation in response to behavioral rejection by a friend. *Dev Psychol* 2009; 45: 1077-96.
133. Heimberg RG, Liebowitz MR, Hope DA, Schneier FR, Holt CS, Welkowitz LA, Juster HR, Campeas R, Bruch MA, Cloitre M, Fallon B, Klein DF. Cognitive behavioral group therapy vs phenelzine therapy for social phobia: 12-week outcome. *Arch Gen Psychiatry* 1998; 55: 1133-41.
134. Noyes R, Jr., Moroz G, Davidson JR, Liebowitz MR, Davidson A, Siegel J, Bell J, Cain JW, Curlik SM, Kent TA, Lydiard RB, Mallinger AG, Pollack MH, Rapaport M, Rasmussen SA, Hedges D, Schweizer E, Uhlenhuth EH. Moclobemide in social phobia: A controlled dose-response trial. *J Clin Psychopharmacol* 1997; 17: 247-54.
135. Stein MB, Liebowitz MR, Lydiard RB, Pitts CD, Bushnell W, Gergel I. Paroxetine treatment of generalized social phobia (social anxiety disorder): A randomized controlled trial. *JAMA* 1998; 280: 708-13.
136. Blanco C, Antia SX, Liebowitz MR. Pharmacotherapy of social anxiety disorder. *Biol Psychiatry* 2002; 51: 109-20.
137. Uzun S, Kozumplik O, Jakovljevic M, Sedic B. Side effects of treatment with benzodiazepines. *Psychiatr Danub* 2010; 22: 90-3.
138. Hedges DW, Brown BL, Shwalb DA, Godfrey K, Larcher AM. The efficacy of selective serotonin reuptake inhibitors in adult social anxiety disorder: A meta-analysis of double-blind, placebo-controlled trials. *J Psychopharmacol* 2007; 21: 102-11.
139. Davidson JR. Pharmacotherapy of social anxiety disorder: What does the evidence tell us? *J Clin Psychiatry* 2006; 67 Suppl 12: 20-6.
140. Knijnik DZ, Kapczinski F, Chachamovich E, Margis R, Eizirik CL. Psychodynamic group treatment for generalized social phobia. *Rev Bras Psiquiatr* 2004; 26: 77-81.
141. Lipsitz JD, Markowitz JC, Cherry S, Fyer AJ. Open trial of interpersonal psychotherapy for the treatment of social phobia. *Am J Psychiatry* 1999; 156: 1814-6.
142. Amir N, Beard C, Taylor CT, Klumpp H, Elias J, Burns M, Chen X. Attention training in individuals with generalized social phobia: A randomized controlled trial. *J Consult Clin Psychol* 2009; 77: 961-73.
143. Ponniah K, Hollon SD. Empirically supported psychological interventions for social phobia in adults: A qualitative review of randomized controlled trials. *Psychol Med* 2008; 38: 3-14.
144. Overholser JC. Cognitive-behavioral treatment of social phobia. *Journal of Contemporary Psychotherapy* 2002; 32: 125-44.
145. Stangier U, Heidenreich T, Peitz M, Lauterbach W, Clark DM. Cognitive therapy for social phobia: Individual versus group treatment. *Behav Res Ther* 2003; 41: 991-1007.

146. Clark DM, Ehlers A, Hackmann A, McManus F, Fennell M, Grey N, Waddington L, Wild J. Cognitive therapy versus exposure and applied relaxation in social phobia: A randomized controlled trial. *J Consult Clin Psychol* 2006; 74: 568-78.

147. Clark DM, Ehlers A, McManus F, Hackmann A, Fennell M, Campbell H, Flower T, Davenport C, Louis B. Cognitive therapy versus fluoxetine in generalized social phobia: A randomized placebo-controlled trial. *J Consult Clin Psychol* 2003; 71: 1058-67.

148. Feske U, Chambless DL. Cognitive behavioral versus exposure only treatment for social phobia: A meta-analysis. *Behav Ther* 1995; 26: 695-720.

149. Taylor S. Meta-analysis of cognitive-behavioral treatments for social phobia. *J Behav Ther Exp Psychiatry* 1996; 27: 1-9.

150. Fedoroff IC, Taylor S. Psychological and pharmacological treatments of social phobia: A meta-analysis. *J Clin Psychopharmacol* 2001; 21: 311-24.

151. Gould RA, Buckminster S, Pollack MH, Otto MW, Massachusetts LY. Cognitive-behavioral and pharmacological treatment for social phobia: A meta-analysis. *Clinical Psychology: Science and Practice* 1997; 4: 291-306.

152. Blanco C, Heimberg RG, Schneier FR, Fresco DM, Chen H, Turk CL, Vermes D, Erwin BA, Schmidt AB, Juster HR, Campeas R, Liebowitz MR. A placebo-controlled trial of phenelzine, cognitive behavioral group therapy, and their combination for social anxiety disorder. *Arch Gen Psychiatry* 2010; 67: 286-95.

153. Mörtberg E, Clark DM, Sundin O, Åberg Wistedt A. Intensive group cognitive treatment and individual cognitive therapy versus treatment as usual in social phobia: A randomized controlled trial. *Acta Psychiatr Scand* 2007; 115: 142-54.

154. Mörtberg E, Karlsson A, Fyring C, Sundin Ö. Intensive cognitive-behavioral group treatment (CBGT) of social phobia: A randomized controlled study. *J Anxiety Disord* 2006; 20: 646-60.

155. Mörtberg E, Clark DM, Sundin Ö, Åberg Wistedt A. Intensive group cognitive treatment and individual cognitive therapy vs. Treatment as usual in social phobia: A randomized controlled trial. *Acta Psychiatr Scand* 2007; 115: 142-54.

156. Blomhoff S, Haug TT, Hellstrom K, Holme I, Humble M, Madsbu HP, Wold JE. Randomised controlled general practice trial of sertraline, exposure therapy and combined treatment in generalised social phobia. *Br J Psychiatry* 2001; 179: 23-30.

157. Davidson JR, Foa EB, Huppert JD, Keefe FJ, Franklin ME, Compton JS, Zhao N, Connor KM, Lynch TR, Gadde KM. Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia. *Arch Gen Psychiatry* 2004; 61: 1005-13.

158. Norberg MM, Krystal JH, Tolin DF. A meta-analysis of d-cycloserine and the facilitation of fear extinction and exposure therapy. *Biol Psychiatry* 2008; 63: 1118-26.

159. Hofmann SG, Meuret AE, Smits JA, Simon NM, Pollack MH, Eisenmenger K, Shiekh M, Otto MW. Augmentation of exposure therapy with d-cycloserine for social anxiety disorder. *Arch Gen Psychiatry* 2006; 63: 298-304.

160. Guastella AJ, Richardson R, Lovibond PF, Rapee RM, Gaston JE, Mitchell P, Dadds MR. A randomized controlled trial of d-cycloserine enhancement of exposure therapy for social anxiety disorder. *Biol Psychiatry* 2008; 63: 544-9.

161. Kraemer HC, Wilson GT, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized clinical trials. *Arch Gen Psychiatry* 2002; 59: 877-83.

162. Keijsers GP, Hoogduin CA, Schaap CP. Predictors of treatment outcome in the behavioural treatment of obsessive-compulsive disorder. *Br J Psychiatry* 1994; 165: 781-6.

163. Ramnerö J. *Behavioral treatments of panic disorder with agoraphobia: Treatment process and determinants of change* [Dissertation]. Stockholm: Stockholm University; 2005.

164. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986; 51: 1173-82.

165. Steketee G, Shapiro LJ. Predicting behavioral treatment outcome for agoraphobia and obsessive compulsive disorder. *Clin Psychol Rev* 1995; 15: 317-46.
166. Hofmann SG, Suvak M. Treatment attrition during group therapy for social phobia. *J Anxiety Disord* 2006; 20: 961-72.
167. de Graaf LE, Hollon SD, Huibers MJ. Predicting outcome in computerized cognitive behavioral therapy for depression in primary care: A randomized trial. *J Consult Clin Psychol* 2010; 78: 184-9.
168. van Beljouw IM, Verhaak PF, Cuijpers P, van Marwijk HW, Penninx BW. The course of untreated anxiety and depression, and determinants of poor one-year outcome: A one-year cohort study. *BMC Psychiatry* 2010; 10: 86.
169. Durham RC, Allan T, Hackett CA. On predicting improvement and relapse in generalized anxiety disorder following psychotherapy. *Br J Clin Psychol* 1997; 36: 101-19.
170. Borge F-M, Hoffart A, Sexton H. Predictors of outcome in residential cognitive and interpersonal treatment for social phobia: Do cognitive and social dysfunction moderate treatment outcome? *J Behav Ther Exp Psychiatry* 2010; 41: 212-9.
171. Eskildsen A, Hougaard E, Rosenberg NK. Pre-treatment patient variables as predictors of drop-out and treatment outcome in cognitive behavioural therapy for social phobia: A systematic review. *Nord J Psychiatry* 2010; 64: 94-105.
172. Mausbach BT, Moore R, Roesch S, Cardenas V, Patterson TL. The relationship between homework compliance and therapy outcomes: An updated meta-analysis. *Cognit Ther Res*; 34: 429-38.
173. Chambless DL, Tran GQ, Glass CR. Predictors of response to cognitive-behavioral group therapy for social phobia. *J Anxiety Disord* 1997; 11: 221-40.
174. Perna G, Favaron E, Di Bella D, Bussi R, Bellodi L. Antipanic efficacy of paroxetine and polymorphism within the promoter of the serotonin transporter gene. *Neuropsychopharmacology* 2005; 30: 2230-5.
175. Malhotra AK, Murphy GM, Jr., Kennedy JL. Pharmacogenetics of psychotropic drug response. *Am J Psychiatry* 2004; 161: 780-96.
176. Bryant RA, Felmingham KL, Falconer EM, Pe Benito L, Dobson-Stone C, Pierce KD, Schofield PR. Preliminary evidence of the short allele of the serotonin transporter gene predicting poor response to cognitive behavior therapy in posttraumatic stress disorder. *Biol Psychiatry* 2010; 67: 1217-9.
177. Soliman F, Glatt CE, Bath KG, Levita L, Jones RM, Pattwell SS, Jing D, Tottenham N, Amso D, Somerville LH, Voss HU, Glover G, Ballon DJ, Liston C, Teslovich T, Van Kempen T, Lee FS, Casey BJ. A genetic variant BDNF polymorphism alters extinction learning in both mouse and human. *Science* 2010; 327: 863-6.
178. Steketee G, Chambless DL. Methodological issues in prediction of treatment outcome. *Clin Psychol Rev* 1992; 12: 387-400.
179. Aiken LS, West SG. *Multiple regression: Testing and interpreting interactions.* London: Sage Publications; 1991.
180. Cartreine JA, Ahern DK, Locke SE. A roadmap to computer-based psychotherapy in the United States. *Harv Rev Psychiatry* 2010; 18: 80-95.
181. Kwan BM, Dimidjian S, Rizvi SL. Treatment preference, engagement, and clinical improvement in pharmacotherapy versus psychotherapy for depression. *Behav Res Ther* 2009; 48: 799-804.
182. Walker J, Vincent N, Furer P, Cox B, Kjernisted K. Treatment preference in hypochondriasis. *J Behav Ther Exp Psychiatry* 1999; 30: 251-8.
183. Marshall WL, Presse L, Andrews WR. A self-administered program for public speaking anxiety. *Behav Res Ther* 1976; 14: 33-9.
184. Marrs RW. A meta-analysis of bibliotherapy studies. *Am J Community Psychol* 1995; 23: 843-70.
185. Rapee RM, Abbott MJ, Baillie AJ, Gaston JE. Treatment of social phobia through pure self-help and therapist-augmented self-help. *Br J Psychiatry* 2007; 191: 246-52.
186. Furmark T, Carlbring P, Hedman E, Sonnenstein A, Clevberger P, Bohman B, Eriksson A, Hallen A, Frykman M, Holmstrom A, Sparthan E, Tillfors M,

Ihrfelt EN, Spak M, Ekselius L, Andersson G. Guided and unguided self-help for social anxiety disorder: Randomised controlled trial. *Br J Psychiatry* 2009; 195: 440-7.

187. Abramowitz JS, Moore EL, Braddock AE, Harrington DL. Self-help cognitive-behavioral therapy with minimal therapist contact for social phobia: A controlled trial. *J Behav Ther Exp Psychiatry* 2009; 40: 98-105.

188. Hedman E, Andersson G, Andersson E, Ljotsson B, Ruck C, Asmundson GJ, Lindefors N. Internet-based cognitive-behavioural therapy for severe health anxiety: Randomised controlled trial. *Br J Psychiatry* 2011; 198: 230-6.

189. Ljótsson B, Falk L, Vesterlund AW, Hedman E, Lindfors P, Rück C, Hursti T, Andreewitch S, Jansson L, Lindefors N, Andersson G. Internet-delivered exposure and mindfulness based therapy for irritable bowel syndrome-a randomized controlled trial. *Behav Res Ther* 2010; 48: 531-9.

190. Ljótsson B, Hedman E, Lindfors P, Hursti T, Lindefors N, Andersson G, Rück C. Long-term follow-up of internet-delivered exposure and mindfulness based treatment for irritable bowel syndrome. *Behav Res Ther* 2011; 49: 58-61.

191. Bouchard S, Paquin B, Payeur R, Allard M, Rivard V, Fournier T, Renaud P, Lapierre J. Delivering cognitive-behavior therapy for panic disorder with agoraphobia in videoconference. *Telemed J E Health* 2004; 10: 13-25.

192. Krijn M, Emmelkamp PM, Olafsson RP, Biemond R. Virtual reality exposure therapy of anxiety disorders: A review. *Clin Psychol Rev* 2004; 24: 259-81.

193. Strom L, Pettersson R, Andersson G. A controlled trial of self-help treatment of recurrent headache conducted via the internet. *J Consult Clin Psychol* 2000; 68: 722-7.

194. Hedman E, Ljótsson B, Rück C, Furmark T, Carlbring P, Lindefors N, Andersson G. Internet administration of self-report measures commonly used in research on social anxiety disorder: A psychometric evaluation. *Computers in Human Behavior* 2010; 26: 736-40.

195. Knaevelsrud C, Maercker A. Internet-based treatment for PTSD reduces distress and facilitates the development of a strong therapeutic alliance: A randomized controlled clinical trial. *BMC Psychiatry* 2007; 7: 13.

196. Spek V, Cuijpers P, Nyklícek I, Riper H, Keyzer J, Pop V. Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: A meta-analysis. *Psychol Med* 2007; 37: 319-28.

197. The Dental and Pharmaceutical Benefits Agency Sweden.:The Dental and Pharmaceutical Benefits Agency Sweden;2011 [cited 2011]; Available from: http://www.tlv.se/tlv/regelverk/.

198. Saha S, Hoerger TJ, Pignone MP, Teutsch SM, Helfand M, Mandelblatt JS. The art and science of incorporating cost effectiveness into evidence-based recommendations for clinical preventive services. *Am J Prev Med* 2001; 20: 36-43.

199. Bravo Vergel Y, Sculpher M. Quality-adjusted life years. *Practical Neurology* 2008; 8: 175-82.

200. King JT, Jr., Tsevat J, Lave JR, Roberts MS. Willingness to pay for a quality-adjusted life year: Implications for societal health care resource allocation. *Med Decis Making* 2005; 25: 667-77.

201. The National Board of Health and Welfare.:The National Board of Health and Welfare; [2011]; Available from: http://www.socialstyrelsen.se/nationellariktlinjerfordepressionochangest.

202. Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. *JAMA: The Journal of the American Medical Association* 1996; 276: 1172-7.

203. Barak A, Klein B, Proudfoot JG. Defining internet-supported therapeutic interventions. *Ann Behav Med* 2009; 38: 4-17.

204. Titov N, Andrews G, Johnston L, Schwencke G, Choi I. Shyness programme: Longer term benefits, cost-effectiveness, and acceptability. *Aust N Z J Psychiatry* 2009; 43: 36-44.

205. Norcross JC, Beutler LE, Levant RF. *Evidence-based practices in mental health: Debate and dialogue on the fundamental questions.* Washington, DC: American Psychological Association; 2006.

206. Flay B, Biglan A, Boruch R, Castro F, Gottfredson D, Kellam S, Mościcki E, Schinke S, Valentine J, Ji P. Standards of evidence: Criteria for efficacy, effectiveness and dissemination. *Prev Sci* 2005; 6: 151-75.

207. Andrews G, Davies M, Titov N. Effectiveness randomized controlled trial of face to face versus internet cognitive behaviour therapy for social phobia. *Aust N Z J Psychiatry* 2011.

208. Titov N, Andrews G, Schwencke G, Solley K, Johnston L, Robinson E. An RCT comparing effect of two types of support on severity of symptoms for people completing internet-based cognitive behaviour therapy for social phobia. *Aust N Z J Psychiatry* 2009; 43: 920-6.

209. Tillfors M, Carlbring P, Furmark T, Lewenhaupt S, Spak M, Eriksson A, Westling BE, Andersson G. Treating university students with social phobia and public speaking fears: Internet delivered self-help with or without live group exposure sessions. *Depress Anxiety* 2008; 25: 708-17.

210. Titov N, Andrews G, Choi I, Schwencke G, Mahoney A. Shyness 3: Randomized controlled trial of guided versus unguided internet-based CBT for social phobia. *Aust N Z J Psychiatry* 2008; 42: 1030-40.

211. Titov N, Andrews G, Schwencke G, Drobny J, Einstein D. Shyness 1: Distance treatment of social phobia over the internet. *Aust N Z J Psychiatry* 2008; 42: 585-94.

212. Titov N, Andrews G, Schwencke G. Shyness 2: Treating social phobia online: Replication and extension. *Aust N Z J Psychiatry* 2008; 42: 595-605.

213. Titov N, Andrews G, Choi I, Schwencke G, Johnston L. Randomized controlled trial of web-based treatment of social phobia without clinician guidance. *Aust N Z J Psychiatry* 2009; 43: 913-9.

214. Aydos L, Titov N, Andrews G. Shyness 5: The clinical effectiveness of internet-based clinician-assisted treatment of social phobia. *Australas Psychiatry* 2009; 17: 488-92.

215. Titov N, Andrews G, Schwencke G, Robinson E, Peters L, Spence J. Randomized controlled trial of internet cognitive behavioural treatment for social phobia with and without motivational enhancement strategies. *Aust N Z J Psychiatry* 2010; 44: 938-45.

216. Berger T, Hohl E, Caspar F. Internet-based treatment for social phobia: A randomized controlled trial. *J Clin Psychol* 2009; 65: 1021-35.

217. Berger T, Caspar F, Richardson R, Kneubuhler B, Sutter D, Andersson G. Internet-based treatment of social phobia: A randomized controlled trial comparing unguided with two types of guided self-help. *Behav Res Ther* 2011; 49: 158-69.

218. Cuijpers P, Schuurmans J. Self-help interventions for anxiety disorders: An overview. *Curr Psychiatry Rep* 2007; 9: 284-90.

219. Svanborg P, Åsberg M. A new self-rating scale for depression and anxiety states based on the comprehensive psychopathological rating scale. *Acta Psychiatr Scand* 1994; 89: 21-8.

220. First MB, Spitzer RL, Gibbon M, Williams JBW, eds. Structured clinical interview for DSM-IV-tr axis I disorders, research version, patient edition. New York: Biometrics Research, New York State Psychiatric Institute; 2002.

221. Fresco DM, Coles ME, Heimberg RG, Liebowitz MR, Hami S, Stein MB, Goetz D. The Liebowitz Social Anxiety Scale: A comparison of the psychometric properties of self-report and clinician-administered formats. *Psychol Med* 2001; 31: 1025-35.

222. Mattick RP, Clarke JC. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. *Behav Res Ther* 1998; 36: 455-70.

223. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: Psychometric properties. *J Consult Clin Psychol* 1988; 56: 893-7.

224. Frisch MB, Cornell J, Villanueva M, Retzlaff PJ. Clinical validation of the quality of life inventory. A measure of life satisfaction for use in treatment planning and outcome assessment. *Psychol Assess* 1992; 4: 92-101.

225. McAlister FA, Sackett DL. Active-control equivalence trials and antihypertensive agents. *Am J Med* 2001; 111: 553-8.

226. Liebowitz MR. Social phobia. *Mod Probl Pharmacopsychiatry* 1987; 22: 141-73.

227. Reiss S, Peterson RA, Gursky DM, McNally RJ. Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behav Res Ther* 1986; 24: 1-8.

228. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The mini-international neuropsychiatric interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; 59 Suppl 20: 22-33.

229. Borkovec TD, Nau SD. Credibility of analogue therapy rationales. *J Behav Ther Exp Psychiatry* 1972; 3: 257-60.

230. Ledley DR, Heimberg RG, Hope DA, Hayes SA, Zaider TI, Dyke MV, Turk CL, Kraus C, Fresco DM. Efficacy of a manualized and workbook-driven individual treatment for social anxiety disorder. *Behav Ther* 2009; 40: 414-24.

231. Hofmann SG, Smits JA. Cognitive-behavioral therapy for adult anxiety disorders: A meta-analysis of randomized placebo-controlled trials. *J Clin Psychiatry* 2008; 69: 621-32.

232. Gueorguieva R, Krystal JH. Move over anova: Progress in analyzing repeated-measures data and its reflection in papers published in the archives of general psychiatry. *Arch Gen Psychiatry* 2004; 61: 310-7.

233. Jacobson NS, Truax P. Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol* 1991; 59: 12-9.

234. Barrett PM, Duffy AL, Dadds MR, Rapee RM. Cognitive-behavioral treatment of anxiety disorders in children: Long-term (6-year) follow-up. *J Consult Clin Psychol* 2001; 69: 135-41.

235. Heimberg RG, Salzman DG, Holt CS, Blendell KA. Cognitive-behavioral group treatment for social phobia: Effectiveness at five-year followup. *Cognitive Ther Res* 1993; 17: 325-39.

236. Saavedra LM, Silverman WK, Morgan-Lopez AA, Kurtines WM. Cognitive behavioral treatment for childhood anxiety disorders: Long-term effects on anxiety and secondary disorders in young adulthood. *J Child Psychol Psychiatry* 2010; 51: 924-34.

237. Fava GA, Rafanelli C, Grandi S, Canestrari R, Morphy MA. Six-year outcome for cognitive behavioral treatment of residual symptoms in major depression. *Am J Psychiatry* 1998; 155: 1443-5.

238. Carlbring P, Nordgren LB, Furmark T, Andersson G. Long-term outcome of internet-delivered cognitive-behavioural therapy for social phobia: A 30-month follow-up. *Behav Res Ther* 2009; 47: 848-50.

239. Michelson L, Mavissakalian M, Marchione K, Dancu C, Greenwald M. The role of self-directed in vivo exposure in cognitive, behavioral, and psychophysiological treatments of agoraphobia. *Behav Ther* 1986; 17: 91-108.

240. Guy W, ed. Clinical global impressions. Rockville: US Department of Health and Human services; 1976.

241. Crippa JAS, De Lima Osório F, Del-Ben CM, Filho AS, Da Silva Freitas MC, Loureiro SR. Comparability between telephone and face-to-face structured clinical interview for DSM-IV in assessing social anxiety disorder. *Perspect Psychiatr Care* 2008; 44: 241-7.

242. Rohde P, Lewinsohn PM, Seeley JR. Comparability of telephone and face-to-face interviews in assessing axis I and II disorders. *Am J Psychiatry* 1997; 154: 1593-8.

243. Hunt C, Andrews G. Long-term outcome of panic disorder and social phobia. *J Anxiety Disord* 1998; 12: 395-406.

244. Hakkaart-van Roijen L, Donker MCH. Manual/imta questionnaire for costs associated with psychiatric illness (TIC-P). 2002; Available from: http://hdl.handle.net/1765/1337.

245. Drummond MF, Sculpher MJ, Torrence GW, O'Brien BJ, Stoddart GL. *Methods for the evaluation of health care programmes.* Oxford: Oxford University Press; 2005.

246. Heimberg RG, Horner KJ, Juster HR, Safren SA, Brown EJ, Schneier FR, Liebowitz MR. Psychometric properties of the Liebowitz Social Anxiety Scale. *Psychol Med* 1999; 29: 199-212.

247. EuroQol-Group. Euroqol - a new facility for the measurement of health-related quality of life. *Health Policy* 1990; 16: 199-208.

248. Efron B, Tibshirani RJ. *An introduction to the bootstrap.* New York: Chapman & Hall; 1993.

249. Little JDC. A proof for the queing formula:$L=\lambda w$. *Oper Res* 1961; 9: 383-7.

250. Reich J, Goldenberg I, Vasile R, Goisman R, Keller M. A prospective follow-along study of the course of social phobia. *Psychiatry Res* 1994; 54: 249-58.

251. Patel A, Rendu A, Moran P, Leese M, Mann A, Knapp M. A comparison of two methods of collecting economic data in primary care. *Fam Pract* 2005; 22: 323-7.

252. Gustavsson JP, Bergman H, Edman G, Ekselius L, Knorring Lv, Linder J. Swedish universities scales of personality (SSP): Construction, internal consistency and normative data. *Acta Psychiatr Scand* 2000; 102: 217-25.

253. First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin LS. *Structured clinical interview for DSM-IV axis II personality disorders, (SCID-II).* Washington, D.C.: American Psychiatric Press, Inc.; 1997.

254. Lindblom B, Holmlund G. Rapid DNA purification for restriction fragment length polymorphism analysis. *Gene Anal Tech* 1988; 5: 97-101.

255. Holmbeck GN. Toward terminological, conceptual, and statistical clarity in the study of mediators and moderators: Examples from the child-clinical and pediatric psychology literatures. *J Consult Clin Psychol* 1997; 65: 599-610.

256. Andreescu C, Mulsant BH, Houck PR, Whyte EM, Mazumdar S, Dombrovski AY, Pollock BG, Reynolds CF, III. Empirically derived decision trees for the treatment of late-life depression. *Am J Psychiatry* 2008; 165: 855-62.

257. Kraemer HC, Lowe KK, Kupfer DJ. *To your health.* New York: Oxford University Press; 2005.

258. Rytwinski NK, Fresco DM, Heimberg RG, Coles ME, Liebowitz MR, Cissell S, Stein MB, Hofmann SG. Screening for social anxiety disorder with the self-report version of the Liebowitz Social Anxiety Scale. *Depress Anxiety* 2009; 26: 34-8.

259. Munoz SR, Bangdiwala SI. Interpretation of kappa and b statistics measures of agreement. *Journal of Applied Statistics* 1997; 24: 105 - 12.

260. Botella C, Gallego MJ, Garcia-Palacios A, Guillen V, Banos RM, Quero S, Alcaniz M. An internet-based self-help treatment for fear of public speaking: A controlled trial. *Cyberpsychol Behav Soc Netw* 2010; 13: 407-21.

261. Titov N, Andrews G, Kemp A, Robinson E. Characteristics of adults with anxiety or depression treated at an internet clinic: Comparison with a national survey and an outpatient clinic. *PLoS ONE* 2010; 5: e10885.

262. Waller G. Evidence-based treatment and therapist drift. *Behav Res Ther* 2009; 47: 119-27.

263. Yonkers KA, Bruce SE, Dyck IR, Keller MB. Chronicity, relapse, and illness - course of panic disorder, social phobia, and generalized anxiety disorder: Findings in men and women from 8 years of follow-up. *Depress Anxiety* 2003; 17: 173-9.

264. The Swedish Council of Health Technology and Assessment [2011]; Available from: http://www.sbu.se/sv/Evidensbaserad-vard/Faktaruta-1-Studiekvalitet-och-evidensstyrka/.