

BMJ Open

Long-term effectiveness and outcome predictors of therapist-guided internet-based cognitive behaviour therapy for social anxiety disorder in routine psychiatric care

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2015-007902
Article Type:	Research
Date Submitted by the Author:	10-Feb-2015
Complete List of Authors:	El Alaoui, Samir; Karolinska Institutet, Department of Clinical Neuroscience Hedman, Erik; Karolinska Institutet, Department of Clinical Neuroscience Ljótsson, Brjánn; Karolinska Institutet, Department of Clinical Neuroscience Lindfors, Nils; Karolinska Institutet, Department of Clinical Neuroscience
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Evidence based practice
Keywords:	PSYCHIATRY, Adult psychiatry < PSYCHIATRY, Anxiety disorders < PSYCHIATRY

SCHOLARONE™
Manuscripts

Long-term effectiveness and outcome predictors of therapist-guided internet-based cognitive behaviour therapy for social anxiety disorder in routine psychiatric care

Samir El Alaoui ¹*, Erik Hedman ^{1,2,3}, Brjánn Ljótsson ^{1,3} & Nils Lindefors ¹

¹ Department of Clinical Neuroscience, Division of Psychiatry, Karolinska Institutet, Stockholm, Sweden

² Department of Clinical Neuroscience, Osher Center for Integrative Medicine & Division of Psychology, Karolinska Institutet, Stockholm, Sweden

³ Department of Clinical Neuroscience, Division of Psychology, Karolinska Institutet, Stockholm

* Address for correspondence

Department of Clinical Neuroscience (CNS), K8, CPF Lindefors, M58, Karolinska Universitetssjukhuset, Huddinge 141 86 Stockholm, Sweden

E-mail: samir.el.alaoui@ki.se

Tel: +46-8-585 866 72

Keywords: Internet, CBT, social anxiety, follow-up, long-term, effectiveness

Word count (excluding title page, abstract, references, figures and tables): 3491

ABSTRACT

Objectives: Although short-term outcome of therapist-guided internet-based cognitive behaviour therapy (ICBT) for treating social anxiety disorder (SAD) has been well studied, little research has been undertaken on the sustainability of treatment gains, especially under clinically representative conditions. Further, there is some debate whether delivering psychological treatment via the internet may be suitable for more severely ill patients.

Design: Longitudinal multilevel growth-modelling of long-term follow-up cohort data.

Setting: An outpatient psychiatric clinic specialised in internet interventions.

Participants: 446 adults having been treated for SAD

Primary and secondary outcome measures: Primary outcomes were estimated improvement rate and Cohen's *d* effect size on the self-rated Liebowitz Social Anxiety Scale. Secondary outcome measures were change in co-morbid depressive symptoms and quality of life.

Results: A large treatment effect was observed on the primary outcome measure after treatment ($d = 0.8$ [95% CI 0.7-0.9]), with continued improvements for up to four years. However, the rate of change varied significantly between individuals over time. A faster rate of improvement was observed among patients with higher illness severity, whereas having a family history of social anxiety was related to worse response.

Conclusions: These findings provide strong evidence for the long-term effectiveness of ICBT for SAD in routine clinical practice, even for more severe cases.

Strengths and limitations of this study:

- Strengths: Large sample, naturalistic setting, includes outcome predictors, using state-of-the-art statistical analyses, reports side-effects of treatment
- Limitations: no comparison group, hard to measure treatment adherence accurately

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **Long-term effectiveness and outcome predictors of therapist-guided internet-based**
2 **cognitive behaviour therapy for social anxiety disorder in routine psychiatric care**

4 **INTRODUCTION**

5 Social anxiety disorder (SAD) is one of the most common anxiety disorders [1] and often
6 follows a chronic course if untreated.[2] The core of SAD is a debilitating fear of negative
7 evaluation causing considerable distress in social situations, reduced quality of life and
8 functional impairment for affected individuals.[3] Conventional face-to-face cognitive-
9 behaviour therapies (CBT) are among the most established and well-researched psychological
10 treatments for SAD.[4] However, there are a number of barriers to treatment such as limited
11 availability of trained therapists, stigma, costs of treatment, and practical difficulties of
12 attending treatment (e.g. taking time off work and geographical distance from treatment
13 facility).[5]

15 To increase accessibility, therapist-guided internet-based CBT (ICBT) has been shown to be a
16 promising method of delivering evidence-based psychotherapies, with demonstrated efficacy
17 in reducing symptoms and with effect sizes comparable to conventional face-to-face CBT.[6]
18 Also, a review of 21 studies reported large within-group effect sizes for both guided and
19 unguided internet-based interventions for SAD. [7] Although sustained effects of ICBT have
20 been reported for up to five years after treatment, those results are only reported from clinical
21 trials.[8-10] Therefore, more knowledge on the long-term effectiveness of ICBT for SAD in
22 naturalistic settings (i.e. when delivered as part of routine clinical practice) is needed since the
23 context of routine care may differ significantly from the context of controlled trials with
24 respect to factors such as selection criteria, monitoring of patients and staff motivation.[11]

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

4.

Identifying factors that can predict non-responders or explain individual differences in long-term improvement is an important addition to the knowledge of how ICBT works in the treatment of SAD within a routine clinical context. Indeed, knowledge about predictors can be of high value to the clinician when making treatment recommendations. For example, the level of baseline illness severity has frequently been linked to higher post-treatment symptom levels after face-to-face CBT [12] or after ICBT [13] and less response to pharmacotherapy or face-to-face CBT.[14] Further, both treatment credibility and adherence appear to be relatively stable predictors of greater short-term response to ICBT [15 16] but little is known whether these factors can predict long-term effects as well. Finally, having a family history of social anxiety has been linked to lower probability of improving after ICBT.[13] Investigating the long-term prognostic value of these factors would increase our understanding on how ICBT works in naturalistic settings for different subgroups of patients.

The main objective of this study was to evaluate the long-term effectiveness of ICBT for SAD in a cohort of consecutively recruited patients treated within routine psychiatric care. Improvements in quality of life and comorbid depressive symptoms were also studied. A secondary aim was to test the prognostic value of illness severity, adherence, treatment credibility, and the influence of having a family history of social anxiety.

METHODS**Participants**

This was a longitudinal study investigating adult patients (N = 446) who had been treated for SAD as part of routine care. In general, patients had to meet the following criteria at the time of inclusion: a) fulfilling DSM-IV criteria of social anxiety disorder, b) agreeing not to undergo concurrent psychological treatments for the duration of ICBT, c) having a stabilized

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

51 dose of psychotropic medication for four weeks if on medication, d) being able to read and
52 write, e) be ≥ 18 years old, f) not present with other psychiatric difficulties (e.g. on-going
53 substance abuse or a psychotic syndrome) and g) having access to a computer or other device
54 with an internet connection.

55

56 **Procedure and design**

57 Treatment and data collection were performed within the context of a publicly funded
58 psychiatric clinic specialized in delivering therapist-guided CBT in the administration format
59 of internet-delivered interventions. As such, no conventional face-to-face treatments are
60 offered. The clinic is part of a university hospital and operates as a conventional psychiatric
61 outpatient clinic. Just as in conventional psychiatric outpatient settings in Sweden, the care is
62 subsidized and patients who show insufficient treatment response may be referred elsewhere
63 for additional treatment. The majority of those seeking treatment were self-referrals, but could
64 also be referred by their GP. Before inclusion, patients underwent a live structured diagnostic
65 interview conducted by a psychiatrist or a resident doctor under supervision. Licensed
66 psychologists guided patients online during twelve weeks. The treatment content was
67 accessible in the form of text modules (similar to chapters in a self-help treatment manual)
68 when logged in onto the program and gained access to one module at a time. As therapists
69 regularly provided feedback on homework associated with each module, they could monitor
70 each patient's progress and provide individual support throughout treatment. In addition, there
71 were weekly assessments of social anxiety and depressive symptoms.

72

73 Patients who had been discharged between October 2010 and June 2013 were informed of the
74 study and invited to complete online long-term follow-up assessments, which have previously
75 been documented as a valid administration format. [17] The study comprised a total of four

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

6.

measurement occasions: (1) at pre-treatment, (2) at post-treatment, (3) at six-month-follow-up and (4) at long-term follow-up spanning a period of approximately one to four years after treatment. The study, including its consent procedure, was approved by the Regional Ethical Review Board in Stockholm, Sweden (no 2011/2091-31/3).

Outcome Measures*Social anxiety*

The self-report version of the Liebowitz Social Anxiety Scale (LSAS-SR) [18] was used as the primary outcome measure. The LSAS-SR has been reported to have a high internal consistency with a Cronbach's alpha of .95 as well as a high 12-week test-retest reliability ($r = .83$). [18 19] At baseline, the LSAS-SR alpha for the present sample was .95.

Comorbid depression

The Montgomery Åsberg Depression Rating Scale Self-Rated [20] (MADRS-S) was used to assess change in depressive symptoms as a secondary outcome measure. MADRS-S measures nine clinical characteristics of depression and the total score scale range is 0 to 54. The test-retest reliability of MADRS-S has been shown to be high ($r = .80-.94$) [20] and Cronbach's alpha for the sample at baseline was .87.

Health-related quality of life

Quality of life was evaluated using the EuroQol (EQ-5D). [21] Five health domains were assessed, namely mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D has demonstrated acceptable psychometric properties and good construct validity. [22]

Potential Prognostic Variables

Baseline illness severity was rated by clinicians on a 7-point scale with the Clinical Global Impression – Severity Scale (CGI-S).[23] The Treatment Credibility Scale [24] measured the perceived credibility and expectancies of the ICBT, operationalized as the total score of patients’ attitudes to the credibility of the treatment and expectancy regarding treatment effectiveness were rated on a 10-point scale (0 = not at all to 10 = very much) after the first week of the treatment. Treatment adherence was defined as the number of modules that the patient had been able to work with during therapy as part of the treatment program, and such measured at post-treatment. Finally, having a family history of social anxiety was coded as a categorical variable during the diagnostic interview conducted by a clinician prior to treatment.

Adverse Events

Data on adverse events were collected during the long-term follow-up assessment in order to identify whether ICBT might have provided any short- or long-term side effects. An “adverse event” was operationalized as any negative experience that patient’s subjectively attributed to the ICBT intervention. Patients were asked to report these events including an option to describe them in free text. Also, they were asked to rate on a four-point Likert scale the degree of which these adverse events affected their well-being (i) when they occurred and (ii) to what degree they presently affected their well-being.

Statistical Analyses

Symptomatic change was analysed using longitudinal multilevel modelling. This approach has the benefit of taking into account the hierarchical nature of repeated measurements (i.e. the dependency of observations of outcome scores clustered within each patient who provided

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

8.

repeated data). Two separate multilevel models were estimated: (i) a longitudinal growth model investigating the overall symptomatic change over time, and (ii) a longitudinal growth model investigating individual differences in the rate of change (i.e. the effect of potential prognostic variables). In both models, an autoregressive structure for the repeated measurements level was used as recommended in longitudinal studies where correlations between measurements tend to weaken as time between them increases [25].

Some methodological choices were made prior to analysis. Two approaches to treating time were tested and compared in regard to goodness of fit to observed data, using the -2 log likelihood ratio test; (i) either grouping measurements into four measurement occasions (i.e. pre-treatment, post-treatment, 6-month-follow-up and long-term follow-up) or (ii) using actual days since treatment start. Grouping measurements yielded a better fit, consequently this approach was used. Further, since the aim of this study was to understand the sustainability of effects after completing treatment, a piecewise treatment of time was conducted. By using a piecewise growth model, two growth curves may be fitted in the same model, where each curve represents each developmental stage in the study (i.e. treatment phase and follow-up phase). Piece 1 (T_1) therefore constituted the phase between pre- and post-treatment and piece 2 (T_2) spanned the period between post-treatment, 6-month-follow-up and long-term follow-up. For the T_1 time variable, the four measurement occasions were coded as 0 1 1 1, and for the T_2 time variable, measurement occasions were coded as 0 0 1 2. The benefit of this approach was that we were able to test whether there was a significant linear trend of continued improvement or worsening of symptoms after having completed treatment.

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

9.

The multilevel model testing the effect of outcome predictors included simultaneous entry of the following measurements: baseline CGI-S, level of adherence, treatment credibility and presence of family history of social anxiety. Consequently, the effect of each prognostic factor was estimated while controlling for the effects of the others. Predictor variables were standardized prior to analysis to facilitate comparison between effects measured on different scales.

Within-group Cohen's d effect sizes for mean differences were calculated using estimated means and observed standard deviations and correlations between the repeated measurements.

Missing Data Analysis

Multilevel modelling provides several benefits in the treatment of missing data. As opposed to traditional complete case analyses where cases having incomplete data are deleted from the analysis, multilevel models incorporate all available data. Therefore, all patients who provided at least one outcome measurement were included in the analyses. All models were fitted using maximum likelihood estimation which calculates estimates of the statistical parameters most likely to have produced the observed data.[26]

In order to investigate any relationship between post-measurements and missing data at long-term follow-up, an independent-samples t-test was performed comparing mean post-treatment LSAS-SR among those who provided long-term follow-up data with those who were lost to long-term follow-up.

RESULTS

Sample Description

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

10.

175 Patient characteristics are presented in Table 1. The sample comprised 446 subjects. Follow-
 176 up assessments were completed at 1.2 to 4.1 years from baseline (M = 2.66, SD = 0.80).

177

178 Table 1. *Description of the participants.*

Variable		
Gender	Women	54.9%
	Men	45.1%
Age	Mean age (SD)	32.67 (9.71)
	Min-max	18-63
Education ^a	7-9 years in school	1.9
	Incomplete vocational or secondary school	4.9
	Vocational school	3.0
	Secondary school	24.5
	University. started but not completed studies	23.1
	University. completed studies	42.5
Marital status	Married or de facto	54.5%
Parental status	Parent (yes)	33%
Social anxiety (pre-treatment)	LSAS clinician rated	66.56 (22.59)
	LSAS self-rated	69.27 (23.23)
Treatment adherence	Mean number of activated modules (SD)	8 (3.35)
Treatment Credibility Scale	Mean score on Treatment Credibility Scale (SD)	36.24 (7.53)
Time since debut of first SAD symptoms, years (SD)		15.93 (10.64)
Global functioning	GAF-score (SD)	61.65 (7.29)
CGI-S Global Severity	Mean CGI-S score (SD)	3.79 (0.83)
	Normal. not at all ill	0%
	Borderline mentally ill	4%
	Mildly ill	35%
	Moderately ill	41%
	Markedly ill	19%
	Severely ill	1%
Co-morbid depression	Extremely ill	0%
	MADRS clinician rated (SD)	15.21 (8.00)
	MADRS-S self-rated (SD)	14.56 (7.75)
Currently on psychotropic medication for SAD		180 (46.8%)
Change of medication after ICBT	No change. Neither during ICBT or after	189 (58.9%)
	No change. Had medication	51 (15.9%)

	during ICBT. and still do	
	Yes. Medication during ICBT but not now	27 (8.4%)
	Yes. No medication during ICBT. but currently on medication	54 (16.8%)
Other psychological treatment after ICBT	No	254 (79.1%)
	Cognitive behavioural therapy (CBT)	47 (14.6%)
	Psychodynamic therapy	6 (1.9%)
	Other structured psychological therapy	14 (4.4%)
Frequency distribution (days to follow-up)	Mean (SD)	971 (293)
	Minimum	441
	Maximum	1492
	25 th percentile	683
	50 th percentile	1006
	75 th percentile	1240

Note: Total N = 446. SAD, social anxiety disorder. CBT, Cognitive Behaviour Therapy. ICBT, Internet-based Cognitive Behaviour Therapy. CGI-S, The Clinical Global Impression - Severity scale. SD, standard deviation. LSAS-SR; Liebowitz Social Anxiety Disorder Scale - self-rated. MADRS-S; Montgomery–Asberg Depression Rating Scale score - self-rated.

^a Level of education was rated on a 7-point scale (1= less than 7-9 years in school; 2 = 7-9 years in school; 3 = incomplete vocational or secondary school; 4 = vocational school; 5 = secondary school; 6 = university, started but not completed studies; 7 = completed university studies).

Attrition and Adherence

Of 446 patients who provided baseline measurements, 391 (88%) provided post-treatment data, 173 (39%) patients provided six-month follow-up data and 321 (72%) provided long-term follow-up data on the main outcome measure. The mean level of treatment adherence was 8 (SD = 3.35) of 12 modules activated.

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

12.

195 **Multilevel Models of Long-term Symptomatic Improvement**

196 Piecewise growth models that included a random intercept, a random linear slope for the
197 treatment phase (piece 1) and a fixed linear slope for the post-treatment to long-term follow-
198 up phase (piece 2) were estimated for LSAS-SR, MADRS-S and EQ-5D. Model-implied
199 means and mean differences and observed standard deviations are presented together with
200 associated effect sizes in Table 2.

Table 2. Estimated parameters from growth curve analysis of continuous outcomes.

Measure	Pre	Post	6MFU	LFU	Effect sizes (Cohen's <i>d</i>) with 95% CI			Rate of change	
	M (SD)	M (SD)	M (SD)	M (SD)	Pre to Post	Pre to 6MFU	Pre to LFU	Pre to Post	Post to LFU
								β 95% CI	β 95% CI
LSAS-SR	69.07 (22.90)	50.38 (24.37)	46.13 (26.21)	41.87 (24.24)	0.79 [0.69, 0.89]	0.92 [0.75, 1.09]	1.17 [1.02, 1.32]	-18.69*** [-20.63,-16.74]	-4.26*** [-5.33,-3.09]
MADRS-S	14.57 (7.62)	9.78 (8.03)	9.63 (9.11)	9.48 (7.97)	0.61 [0.52, 0.70]	0.59 [0.42, 0.75]	0.67 [0.54, 0.80]	-4.78*** [-5.45,-4.12]	-0.15 [-0.59,-0.28]
EQ-5D	0.81 (0.13)	0.82 (0.15)	0.83 (0.18)	0.85 (0.18)	-0.12 [-0.22, 0.01]	-0.17 [-0.36, 0.02]	-0.25 [-0.40, -0.10]	0.02* [0.00, 0.03]	0.01* [0.00, 0.02]

Note. Observed means and standard deviations for pre-treatment, and estimated means and observed standard deviations for post-treatment, six-month-follow-up and long-term follow-up are reported. For Cohen's *d*, an effect size of 0.2 is considered to be a small effect, 0.5 a medium effect and > 0.8 a large effect. For slope coefficients of rate of change, significant effects of time on outcome is denoted as ***, *p* < .001; **, *p* < .01 and *, *p* < .05. M, mean; SD, standard deviation; Pre, before treatment; Post, post-treatment; 6MFU, 6 months after treatment; LFU, long-term follow-up 1.2 to 4 years after treatment start; CI, confidence interval; LSAS-SR, Liebowitz Social Anxiety Scale questionnaire-Self-report; MADRS-S, Montgomery Åsberg Depression Rating Scale-Self-report; EQ-5D, Health-Related Quality of Life.

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

14.

There was a significant effect of linear time on all three outcome measures between pre-treatment and post-treatment (piece 1), reflecting large symptomatic improvements on social anxiety, moderate improvements on depression and small improvements on quality of life during the active treatment phase. After treatment (piece 2), continued long-term improvements (i.e. a significant effect of time) were observed on symptoms of social anxiety and quality of life. Also, achieved improvements on symptoms of depression were maintained (i.e. a non-significant effect of time).

Adverse Effects

Of 281 patients that provided data on adverse effects, 22 (7.8%) subjects reported having experienced at least one adverse effect attributed to ICBT. However, 251 (89.3%) subjects responded that regardless of whether or not they had experienced any adverse effect, these were in such cases minor and had no significant effect on them during treatment and 263 (93.6%) reported that they experienced no significant adverse long-term effects. Nine (3.2%) subjects reported that adverse events attributed to the intervention had a very negative acute effect and three (1.1%) reported that these had also very negative long-term effects. Common side-effects described by subjects were experiencing feelings of inadequacy, guilt, stress, worry or failure of not adhering to the treatment schedule (these feelings would often be triggered by receiving reminders from therapists), anxiety associated with exposure assignments and anxiety associated with an increased self-awareness of symptoms, negative cognitions and maladaptive behaviours.

Multilevel Model Explaining Individual Differences in the Rate of Symptomatic Change

Estimates of model parameters predicting individual differences in long-term rate of change in social anxiety symptoms are presented in Table 3 and illustrated in Figures 4 and 5. A

higher level of illness severity (i.e. baseline CGI-S scores) was associated with a faster rate of improvement, whereas having a family history of social anxiety was related to a slower rate of improvement. When CGI-S scores and family history of social anxiety were controlled for, adherence and treatment credibility had no significant predictive value in explaining individual differences in the long-term rate of change.

Table 3. Estimated parameters from growth curve analysis examining the long-term effects of adherence, treatment credibility, illness severity and family history on the rate of symptomatic improvement.

Variables	Estimate	Standard Error	<i>p</i>	95% Confidence Interval	
				Lower Bound	Upper Bound
Intercept	68.47	1.13	***	66.25	70.69
Time	-27.48	1.51	***	-30.45	-24.50
Predictors					
Time × Adherence	-2.29	1.75		-5.73	1.15
Time × Treatment credibility	-2.36	1.57		-5.46	0.74
Time × CGI-S	-6.03	1.53	***	-9.05	-3.01
Time × Family history of social anxiety	3.40	1.45	*	0.55	6.26

Note. *, *p* < 0.05. ***, *p* < 0.001. SE; standard error. Dependent Variable is LSAS-SR.

Predictor variables were standardized prior to analysis to facilitate comparison between effects measured on different scales. Predictor coefficients reflect the effect on the rate of change in social anxiety over the entire study period (from pre-treatment to long-term follow-up). SLSAS-SR; Liebowitz Social Anxiety Disorder Scale - self-rated. CGI-S; The Clinical Global Impression - Severity scale. Adherence was operationalized as the number of activated treatment modules.

Missing Data Analysis

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

16.

To test any association between the level of social anxiety at post-treatment and missing data at long-term follow-up, an independent-samples t-test was performed comparing mean post-treatment LSAS-SR scores among those who provided long-term follow-up data with those who were lost to follow-up. There was no difference in post-treatment LSAS-SR scores between patients who provided follow-up data ($M = 49.08$, $SD = 23.68$) and those who were lost to follow-up ($M = 52.64$, $SD = 26.30$); $t(389) = -1.247$, $p = 0.213$. Also, there was no difference in pre-treatment LSAS-SR scores between patients who provided follow-up data ($M = 69.07$, $SD = 22.23$) and those who were lost to follow-up ($M = 69.18$, $SD = 25.99$); $t(444) = -0.046$, $p = 0.964$.

DISCUSSION

Previous research on the clinical effectiveness of ICBT for SAD has demonstrated large short-term effect sizes [27 28]. The aim of the present study was to determine the sustainability of treatment effects in a naturalistic setting (i.e. routine psychiatric care) and identify factors that may explain individual differences in long-term rate of improvement. We are only aware of three long-term follow-up studies on ICBT for SAD, all of which were clinical trials. In these, large effect sizes were observed after treatment and sustained at 2.5-year follow-up[8], at four-year follow-up [10] and at five-year follow-up[9]. In line with these reports, we have observed similar results in a naturalistic setting; a large treatment effect achieved at post-treatment and that patients, overall, continued to improve for up to four years after treatment.

A secondary aim of this study was to identify prognostic patient characteristics that moderate long-term treatment response. Expanding our knowledge about which patients are more likely to benefit from – or fail in – ICBT might help further refining inclusion guidelines and

modifying treatment strategies to better suit different patient needs. Although adherence and treatment credibility has been associated with better outcome in previous research[15], we have found that these factors lack predictive value over longer follow-up timeframes when illness severity is controlled for. Evidence regarding the prognostic value of baseline illness severity is somewhat inconclusive. For example, one review [29] on outcome predictors of conventional CBT for SAD found that although higher baseline severity predicted higher levels of severity after treatment, it was not related to the degree of improvement whereas another review [30] concluded that greater illness severity predicted a worse response. Consequently, our finding that illness severity is associated with a faster rate of symptomatic improvement is surprising. Nonetheless, this observation is a strong indicator that ICBT is also effective for patients who are severely ill, which may be contrary to common beliefs regarding internet-delivered therapies. We also identified family history of social anxiety as a predictor of poorer outcome. This relationship has been observed in both pharmacological treatment for SAD [31] and in an RCT on ICBT for SAD [13]. Although family history has been shown to be associated with a two- to three-fold risk for developing SAD [32], it is unclear which mediating mechanisms of genetic and environmental factors may be responsible for the variance in treatment effects.

There are some limitations of the study; the most apparent being the lack of a comparison group to control for spontaneous recovery. While this would have been ideal, this was primarily a cohort study conducted within a naturalistic clinical context. As such, the focus of this investigation was principally the symptomatic change over time within the study sample. Further, since this was not a comparative study, it might be unclear as to how comparable this study sample is to a typical SAD sample. However, it seems that the included patients could be considered as representative on a number of variables typical patients with SAD when

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

18.

comparing demographic and clinical characteristics with a large national sample of U.S. adults [33]. For example, our sample reflects gender differences in prevalence (i.e. SAD is slightly more common in women than in men). Also, age of onset is typically around 15 years of age, which reflect our current sample with a mean age of 33 and a mean time since debut of first SAD symptoms of 16 years. Another limitation concerns the operational definition of treatment adherence. This partly concerns defining adherence as the number of activated modules. Since participation and adherence in CBT typically refer to both in-session and out of session behaviour, homework assignments reflect a critical aspect of the treatment package. Therefore, since a new module was activated only after completion of the previous module and its homework assignment, it is probable that many patients did not fully complete their homework assignment related to their last module. However, although the degree of completion of the last activated module is unclear, we still know how many modules they have worked with at a minimum: all *until* the last activated module. Consequently, for some patients the level of adherence may be overrated by 1 (i.e. those who did not complete the last module they had access to. On the other hand, a more serious potential risk of measurement error in regard to measuring adherence is the lack of information regarding how closely the number of modules correlates with actual therapeutic activity.

In sum, this study demonstrates that ICBT for the treatment of SAD in regular clinical practice is effective not only short-term but also long-term. We have also found that higher illness severity is related to a greater rate of improvement, whereas having a family history of social anxiety is related to worse response. Considering that SAD is one of the most common anxiety disorders and that access to CBT is rather limited, ICBT could significantly increase the availability of evidence-based effective treatments for a large patient group.

COMPETING INTERESTS

All authors declare no competing interests.

FUNDING

This study was supported by research grants from Stockholm County Council. It is a public institution and had no role in study design, data collection, analysis, data interpretation, manuscript writing, or decision to submit for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

AUTHOR CONTRIBUTIONS

All authors contributed equally to literature search, figures, study design, data collection, data analysis, data interpretation and writing.

REFERENCES

1. Ruscio AM, Brown TA, Chiu WT, et al. Social fears and social phobia in the USA: results from the National Comorbidity Survey Replication. Psychol Med 2008;**38**(01):15-28
doi: doi:10.1017/S0033291707001699[published Online First: Epub Date]].

2. Reich J, Goldenberg I, Vasile R, et al. A prospective follow-along study of the course of social phobia. Psychiatry Res 1994;**54**(3):249-58

3. Stein MB, Roy-Byrne PP, Craske MG, et al. Functional impact and health utility of anxiety disorders in primary care outpatients. Medical care 2005;**43**(12):1164-70

4. Hofmann SG. Cognitive factors that maintain social anxiety disorder: a comprehensive model and its treatment implications. Cognitive behaviour therapy 2007;**36**(4):193-209 doi: 10.1080/16506070701421313[published Online First: Epub Date]].

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

20.

5. Mewton L, Smith J, Rossouw P, et al. Current perspectives on Internet-delivered cognitive behavioral therapy for adults with anxiety and related disorders. *Psychology research and behavior management* 2014;**7**:37-46 doi: 10.2147/PRBM.S40879[published Online First: Epub Date]].
6. Andersson G, Cuijpers P, Carlbring P, et al. Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis. *World psychiatry : official journal of the World Psychiatric Association* 2014;**13**(3):288-95 doi: 10.1002/wps.20151[published Online First: Epub Date]].
7. Boettcher J, Carlbring P, Renneberg B, et al. Internet-Based Interventions for Social Anxiety Disorder - an Overview. *Verhaltenstherapie* 2013;**23**(3):160-68 doi: Doi 10.1159/000354747[published Online First: Epub Date]].
8. Carlbring P, Nordgren LB, Furmark T, et al. Long-term outcome of Internet-delivered cognitive-behavioural therapy for social phobia: a 30-month follow-up. *Behaviour research and therapy* 2009;**47**(10):848-50 doi: 10.1016/j.brat.2009.06.012[published Online First: Epub Date]].
9. Hedman E, Furmark T, Carlbring P, et al. A 5-Year follow-up of internet-based cognitive behavior therapy for social anxiety disorder. *J Med Internet Res* 2011;**13**(2):e39 doi: 10.2196/jmir.1776[published Online First: Epub Date]].
10. Hedman E, El Alaoui S, Lindefors N, et al. Clinical effectiveness and cost-effectiveness of Internet- vs. group-based cognitive behavior therapy for social anxiety disorder: 4-Year follow-up of a randomized trial. *Behaviour research and therapy* 2014;**59C**:20-29 doi: 10.1016/j.brat.2014.05.010[published Online First: Epub Date]].
11. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical-Evidence of Bias - Dimensions of Methodological Quality Associated with Estimates of Treatment Effects in Controlled

Trials. *Jama-J Am Med Assoc* 1995;**273**(5):408-12 doi: DOI
10.1001/jama.273.5.408[published Online First: Epub Date]].

12. McEvoy PM, Nathan P, Rapee RM, et al. Cognitive behavioural group therapy for social phobia: evidence of transportability to community clinics. *Behaviour research and therapy* 2012;**50**(4):258-65 doi: 10.1016/j.brat.2012.01.009[published Online First: Epub Date]].

13. Hedman E, Andersson E, Ljotsson B, et al. Clinical and genetic outcome determinants of internet- and group-based cognitive behavior therapy for social anxiety disorder. *Acta psychiatrica Scandinavica* 2012;**126**(2):126-36 doi: 10.1111/j.1600-0447.2012.01834.x[published Online First: Epub Date]].

14. Scholing A, Emmelkamp PM. Prediction of treatment outcome in social phobia: a cross-validation. *Behaviour research and therapy* 1999;**37**(7):659-70

15. Nordgreen T, Havik OE, Ost LG, et al. Outcome predictors in guided and unguided self-help for social anxiety disorder. *Behaviour research and therapy* 2012;**50**(1):13-21 doi: 10.1016/j.brat.2011.10.009[published Online First: Epub Date]].

16. El Alaoui S, Hedman E, Ljótsson B, et al. Predictors of Outcome and Adherence in Internet-based Cognitive Behavior Therapy for Social Anxiety Disorder in Routine Psychiatric Care. Unpublished manuscript

17. Hedman E, Ljótsson B, Rück C, et al. 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

18. Baker SL, Heinrichs N, Kim H-J, et al. The Liebowitz Social Anxiety Scale as a self-report instrument: a preliminary psychometric analysis. *Behav Res Ther* 2002;**40**(6):701-15

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

22.

19. Heimberg RG, Horner KJ, Juster HR, et al. Psychometric properties of the Liebowitz Social Anxiety Scale. *Psychol Med* 1999;**29**(01):199-212 doi: doi:10.1017/S0033291798007879[published Online First: Epub Date]].
20. Svanborg P, Asberg M. A new self-rating scale for depression and anxiety states based on the Comprehensive Psychopathological Rating Scale. *Acta psychiatrica Scandinavica* 1994;**89**(1):21-8
21. EuroQol-Group. EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy* 1990;**16**(3):199-208
22. Stark RG, Reitmeir P, Leidl R, et al. Validity, reliability, and responsiveness of the EQ-5D in inflammatory bowel disease in Germany. *Inflamm Bowel Dis* 2010;**16**(1):42-51 doi: 10.1002/ibd.20989[published Online First: Epub Date]].
23. Guy W. Clinical Global Impressions. ECDEU Manual. Rockville, MD: NIMH: US Dept of Health and Human Services, 1976:217-22.
24. Borkovec TD, Nau SD. Credibility of analogue therapy rationales. *Journal of behavior therapy and experimental psychiatry* 1972;**3**(4):257-60
25. Heck RH, Thomas SL, Tabata LN. *Multilevel and longitudinal modeling with IBM SPSS*. Second edition. ed. New York, NY: Routledge, 2013.
26. Hox JJ. *Multilevel analysis : techniques and applications*. 2nd ed. New York: Routledge, 2010.
27. Aydos L, Titov N, Andrews G. Shyness 5: the clinical effectiveness of Internet-based clinician-assisted treatment of social phobia. *Australasian psychiatry : bulletin of Royal Australian and New Zealand College of Psychiatrists* 2009;**17**(6):488-92 doi: 10.1080/10398560903284943[published Online First: Epub Date]].
28. Hedman E, Andersson G, Ljotsson B, et al. Internet-based cognitive behavior therapy vs. cognitive behavioral group therapy for social anxiety disorder: a randomized

controlled non-inferiority trial. PloS one 2011;**6**(3):e18001 doi:
10.1371/journal.pone.0018001[published Online First: Epub Date]].

29. 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. Nordic journal of psychiatry 2010;**64**(2):94-105 doi:
10.3109/08039480903426929[published Online First: Epub Date]].

30. Mululo SC, Menezes GB, Vigne P, et al. A review on predictors of treatment outcome in social anxiety disorder. Revista brasileira de psiquiatria 2012;**34**(1):92-100

31. Slaap BR, van Vliet IM, Westenberg HG, et al. Responders and non-responders to drug treatment in social phobia: differences at baseline and prediction of response. J Affect Disord 1996;**39**(1):13-9

32. Tillfors M, Furmark T, Ekselius L, et al. Social phobia and avoidant personality disorder as related to parental history of social anxiety: a general population study. Behaviour research and therapy 2001;**39**(3):289-98

33. Xu Y, Schneier F, Heimberg RG, et al. Gender differences in social anxiety disorder: results from the national epidemiologic sample on alcohol and related conditions. Journal of anxiety disorders 2012;**26**(1):12-9 doi:
10.1016/j.janxdis.2011.08.006[published Online First: Epub Date]].

FIGURE LEGENDS

Figure 1. Improvement in social anxiety after internet-based cognitive behavioural therapy for social anxiety disorder. Means are estimated from a linear piecewise multilevel growth model, depicted with 95% confidence intervals. LSAS-SR, Liebowitz Social Anxiety Scale questionnaire-Self-report.

Figure 2. Improvement in co-morbid depressive symptoms after internet-based cognitive behavioural therapy for social anxiety disorder. Means are estimated from a linear piecewise multilevel growth model, depicted with 95% confidence intervals. MADRS-S, Montgomery Åsberg Depression Rating Scale-Self-report.

Figure 3. Improvement in health-related quality of life after internet-based cognitive behavioural therapy for social anxiety disorder. Means are estimated from a linear piecewise multilevel growth model, depicted with 95% confidence intervals. EQ-5D, Health-Related Quality of Life.

Figure 4. Predicted long-term symptomatic change based on individual differences in illness severity. Predicted trajectory of social anxiety symptoms after internet-based cognitive behavioural therapy for social anxiety disorder. For illustrative purposes, a categorization was performed to depict predicted growth curves for patients scoring high and low on the Clinical Global Impression - Severity scale. High severity was operationalized as 1 standard deviation above the mean CGI-S score and low credibility as 1 standard deviation below the mean. Mean CGI-S was 3.79 (SD = 0.83). LSAS-SR, Liebowitz Social Anxiety Scale questionnaire-Self-report; CGI-S; The Clinical Global Impression - Severity scale; SD, standard deviation.

Figure 5. Predicted long-term symptomatic change based on individual differences in family history of social anxiety. Predicted growth curves for patients reporting the having a family history of social anxiety. LSAS-SR, Liebowitz Social Anxiety Scale questionnaire-Self-report.

For peer review only

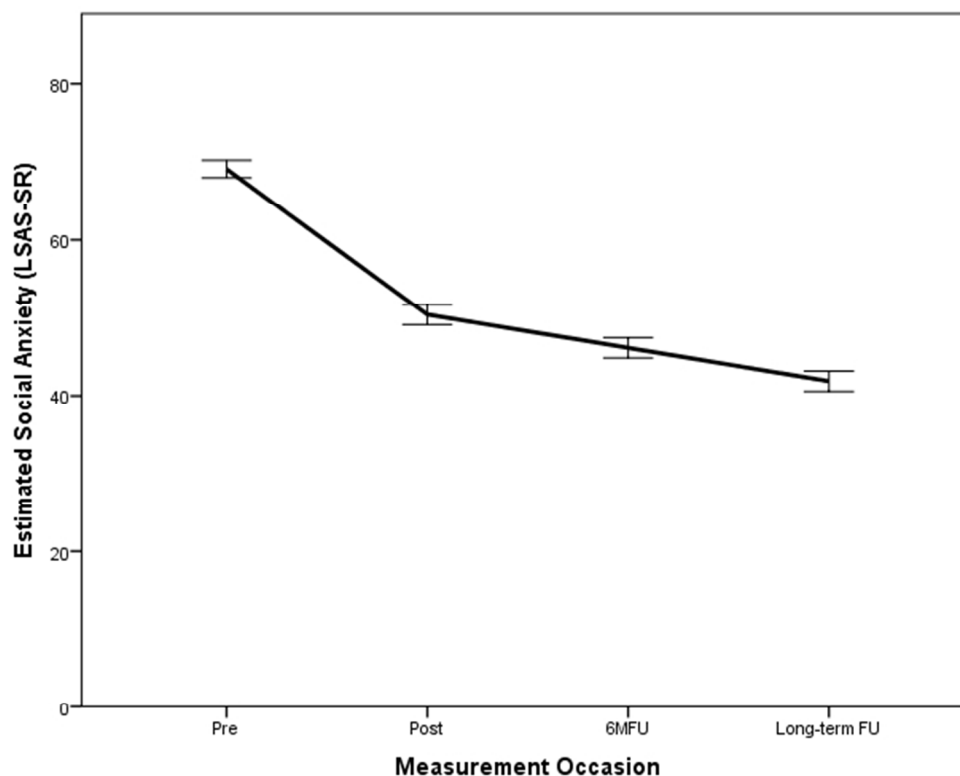


Figure 1. Improvement in social anxiety after internet-based cognitive behavioural therapy for social anxiety disorder. Means are estimated from a linear piecewise multilevel growth model, depicted with 95% confidence intervals. LSAS-SR, Liebowitz Social Anxiety Scale questionnaire-Self-report. 221x177mm (72 x 72 DPI)

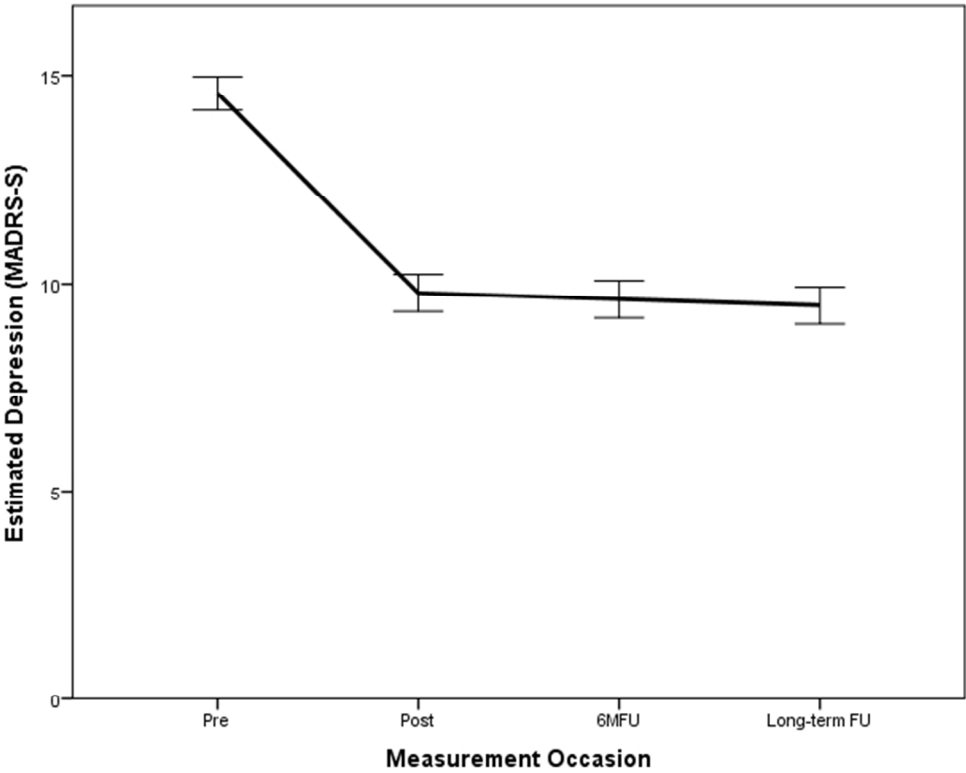


Figure 2. Improvement in co-morbid depressive symptoms after internet-based cognitive behavioural therapy for social anxiety disorder. Means are estimated from a linear piecewise multilevel growth model, depicted with 95% confidence intervals. MADRS-S, Montgomery Åsberg Depression Rating Scale-Self-report. 221x177mm (72 x 72 DPI)

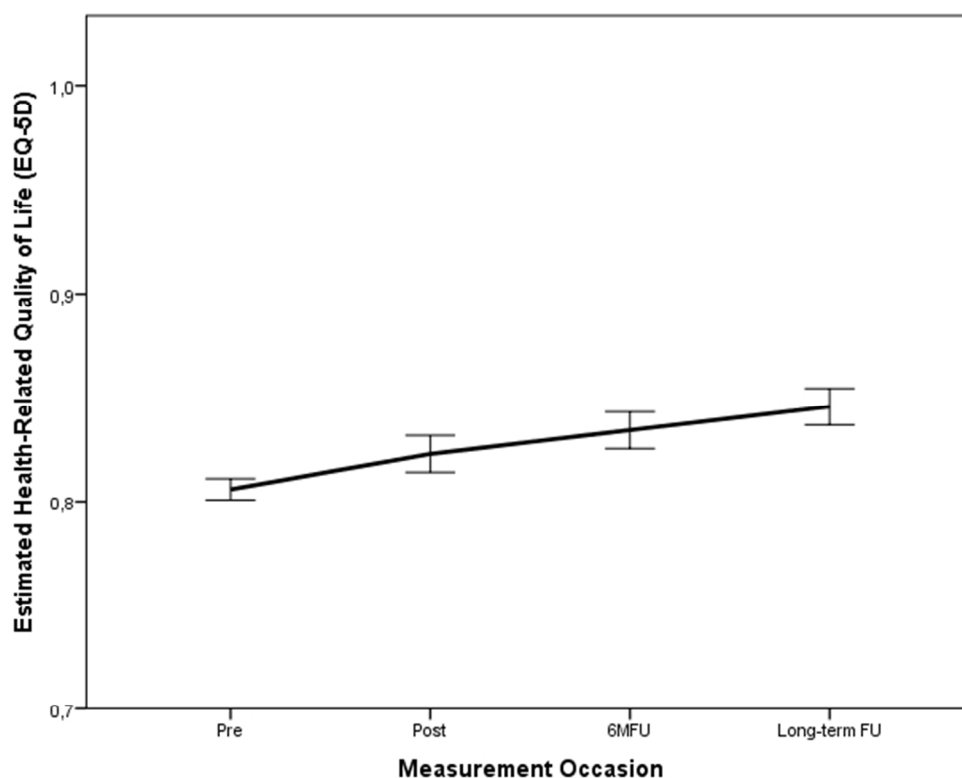


Figure 3. Improvement in health-related quality of life after internet-based cognitive behavioural therapy for social anxiety disorder. Means are estimated from a linear piecewise multilevel growth model, depicted with 95% confidence intervals. EQ-5D, Health-Related Quality of Life.
221x177mm (72 x 72 DPI)

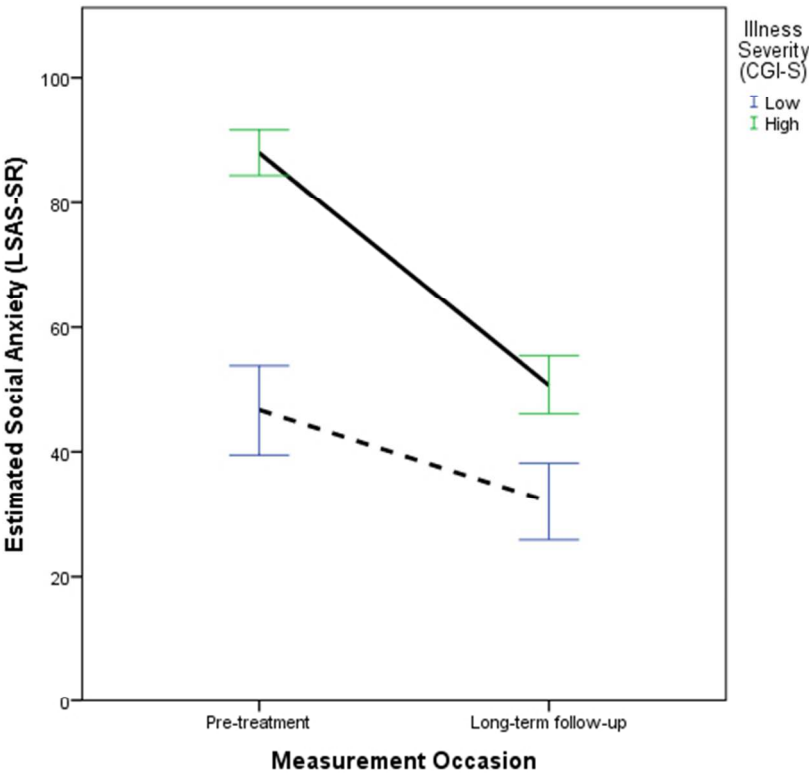


Figure 4. Predicted long-term symptomatic change based on individual differences in illness severity. Predicted trajectory of social anxiety symptoms after internet-based cognitive behavioural therapy for social anxiety disorder. For illustrative purposes, a categorization was performed to depict predicted growth curves for patients scoring high and low on the Clinical Global Impression - Severity scale . High severity was operationalized as 1 standard deviation above the mean CGI-S score and low credibility as 1 standard deviation below the mean. Mean CGI-S was 3.79 (SD = 0.83). LSAS-SR, Liebowitz Social Anxiety Scale questionnaire-Self-report; CGI-S; The Clinical Global Impression - Severity scale; SD, standard deviation. 221x177mm (72 x 72 DPI)

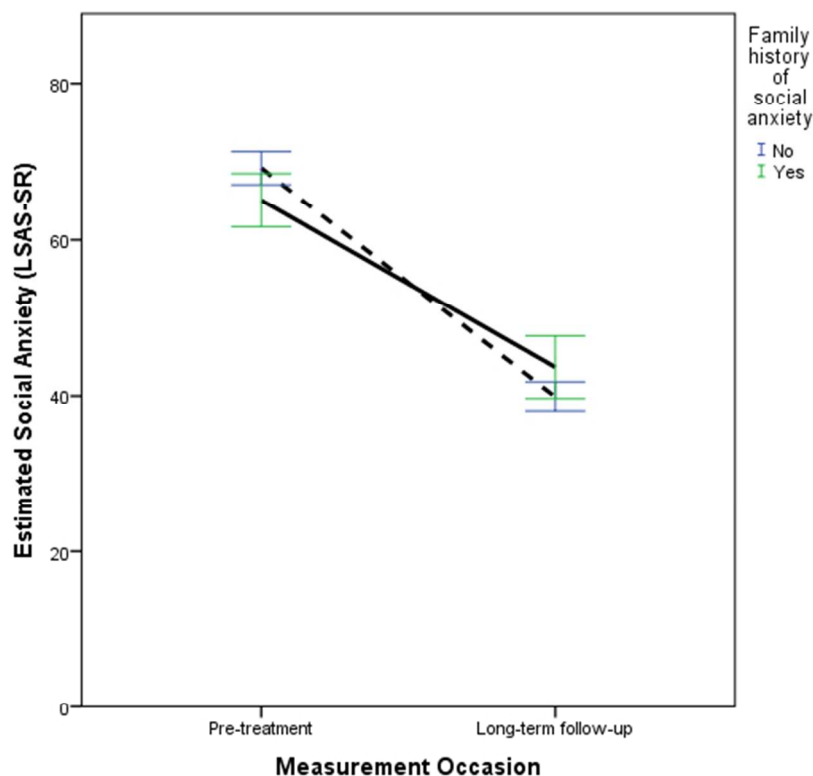


Figure 5. Predicted long-term symptomatic change based on individual differences in family history of social anxiety. Predicted growth curves for patients reporting the having a family history of social anxiety. LSAS-SR, Liebowitz Social Anxiety Scale questionnaire-Self-report.
221x177mm (72 x 72 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants (b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses

Continued on next page

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion

Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
---------	----	---

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Long-term effectiveness and outcome predictors of therapist-guided internet-based cognitive behaviour therapy for social anxiety disorder in routine psychiatric care

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2015-007902.R1
Article Type:	Research
Date Submitted by the Author:	23-Apr-2015
Complete List of Authors:	El Alaoui, Samir; Karolinska Institutet, Department of Clinical Neuroscience Hedman, Erik; Karolinska Institutet, Department of Clinical Neuroscience Ljótsson, Brjánn; Karolinska Institutet, Department of Clinical Neuroscience Lindfors, Nils; Karolinska Institutet, Department of Clinical Neuroscience
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Evidence based practice
Keywords:	PSYCHIATRY, Adult psychiatry < PSYCHIATRY, Anxiety disorders < PSYCHIATRY

SCHOLARONE™
Manuscripts

Long-term effectiveness and outcome predictors of therapist-guided internet-based cognitive behaviour therapy for social anxiety disorder in routine psychiatric care

Samir El Alaoui ¹*, Erik Hedman ^{1,2,3}, Brjánn Ljótsson ^{1,3} & Nils Lindefors ¹

¹ Department of Clinical Neuroscience, Division of Psychiatry, Karolinska Institutet, Stockholm, Sweden

² Department of Clinical Neuroscience, Osher Center for Integrative Medicine, Karolinska Institutet, Stockholm, Sweden

³ Department of Clinical Neuroscience, Division of Psychology, Karolinska Institutet, Stockholm

* Address for correspondence

Department of Clinical Neuroscience (CNS), K8, CPF Lindefors, M58, Karolinska Universitetssjukhuset, Huddinge 141 86 Stockholm, Sweden

E-mail: samir.el.alaoui@ki.se

Tel: +46-8-585 866 72

Keywords: Internet, CBT, social anxiety, follow-up, long-term, effectiveness

Word count (excluding title page, abstract, references, figures and tables): 4266

ABSTRACT

Objectives: Although short-term outcome of therapist-guided internet-based cognitive behaviour therapy (ICBT) for treating social anxiety disorder (SAD) has been well studied, little research has been undertaken on the sustainability of treatment gains, especially under clinically representative conditions. Further, there is some debate whether delivering psychological treatment via the internet may be suitable for more severely ill patients.

Design: Longitudinal multilevel growth-modelling of long-term (1-4 years) follow-up cohort data.

Setting: An outpatient psychiatric clinic specialised in internet interventions.

Participants: 446 adults having been treated for SAD.

Primary and secondary outcome measures: Primary outcomes were estimated improvement rate and Cohen's d effect size on the self-rated Liebowitz Social Anxiety Scale. Secondary outcome measures were change in co-morbid depressive symptoms and health-related quality of life.

Results: A large treatment effect was observed on the primary outcome measure after treatment ($d = 0.8$ [95% CI 0.7, 0.9]), with continued long-term improvements ($d = 1.2$ [95% CI 1.0, 1.3]). However, the rate of change varied significantly between individuals over time. A faster rate of improvement was observed among patients with higher illness severity, whereas having a family history of social anxiety was related to worse response. Long-term improvements were also observed in co-morbid depressive symptoms ($d = 0.7$ [95% CI 0.5, 0.8]) and health-related quality of life ($d = -0.3$ [95% CI -0.4, -0.1]).

Conclusions: These findings provide evidence for the long-term effectiveness of ICBT for SAD in routine clinical practice, even for more severe cases.

Strengths and limitations of this study:

- Strengths: Large sample, naturalistic setting, includes outcome predictors, using state-of-the-art statistical analyses, reports side-effects of treatment
- Limitations: no comparison group, hard to measure treatment adherence accurately

For peer review only

Long-term effectiveness and outcome predictors of therapist-guided internet-based cognitive behaviour therapy for social anxiety disorder in routine psychiatric care

INTRODUCTION

Social anxiety disorder (SAD) is one of the most common anxiety disorders [1] and often follows a chronic course if untreated.[2] The core of SAD is a debilitating fear of negative evaluation causing considerable distress in social situations, reduced quality of life and functional impairment for affected individuals.[3] Conventional face-to-face cognitive-behaviour therapies (CBT) are among the most established and well-researched psychological treatments for SAD.[4] However, there are a number of barriers to treatment such as limited availability of trained therapists, stigma, costs of treatment, and practical difficulties of attending treatment (e.g. taking time off work and geographical distance from treatment facility).[5]

To increase accessibility, therapist-guided internet-based CBT (ICBT) has been shown to be a promising method of delivering evidence-based psychological treatments. This format of delivering CBT may also be particularly advantageous in the treatment of SAD because of the nature of the disorder, especially for patients presenting with greater illness severity who might fear face-to-face interactions with a therapist.[5 6] ICBT may in such cases be preferable for those who might otherwise avoid seeking help. ICBT has demonstrated efficacy in reducing symptoms and with effect sizes comparable to conventional face-to-face CBT.[7] A review of 21 studies reported large within-group effect sizes for both guided and unguided internet-based interventions for SAD. [8] Although sustained effects of ICBT have been reported for up to five years after treatment, these results are reported from clinical trials.[9-11] Although there is evidence that ICBT may be equally effective as group CBT for SAD

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

5.

also under clinically representative conditions [12-14], more knowledge on the long-term effectiveness of ICBT for SAD in naturalistic settings (i.e. when delivered as part of routine clinical practice) is needed since the context of routine care may differ significantly from the context of controlled trials with respect to factors such as selection criteria, monitoring of patients and staff motivation.[15]

Identifying factors that can predict non-responders or explain individual differences in long-term improvement is an important addition to the knowledge of how ICBT works in the treatment of SAD within a routine clinical context. Indeed, knowledge about predictors can be of high value to the clinician when making treatment recommendations. For example, the level of baseline illness severity has frequently been linked to higher post-treatment symptom levels after face-to-face CBT [16] or after ICBT [17] and less response to pharmacotherapy or face-to-face CBT.[18] Further, both treatment credibility and adherence appear to be relatively stable predictors of greater short-term response to ICBT [19 20] but little is known whether these factors can predict long-term effects as well. Finally, having a family history of social anxiety has been linked to lower probability of symptomatic improvement after ICBT.[17] Investigating the long-term prognostic value of these factors would increase our understanding on how ICBT works in naturalistic settings for different subgroups of patients.

The main objective of this study was to evaluate the long-term effectiveness of ICBT for SAD in a cohort of consecutively recruited patients treated within routine psychiatric care. Long-term effects on quality of life and comorbid depressive symptoms were also studied. A secondary aim was to test the prognostic value of illness severity, adherence, treatment credibility, and the influence of having a family history of social anxiety.

METHODS

Participants

This was a longitudinal study investigating adult patients (N = 446) who had a principal diagnosis of SAD and had been treated for SAD as part of routine care. In general, patients had to meet the following criteria at the time of inclusion: a) fulfilling DSM-IV criteria of social anxiety disorder, b) agreeing not to undergo concurrent psychological treatments for the duration of ICBT, c) having a stabilized dose of psychotropic medication for four weeks if on medication, d) be ≥ 18 years old and e) having access to a computer or other device with an internet connection. In general, exclusion from ICBT was based on the following criteria: a) patients with severe depression (clinician rated MADRS ≥ 35) and/or moderate to high risk of suicide where monitoring is required, b) patients with low motivation, severe apathy or difficulty concentrating, c) patients with psychosis, d) patients with untreated drug or alcohol problems that may pose barriers to treatment, e) reading and/or writing difficulties, including language difficulties, and f) patients residing outside the city county.

Procedure and design

Treatment and data collection were performed within the context of a government-funded psychiatric clinic specialized in providing therapist-guided CBT using the internet as the mode of treatment delivery. As such, no conventional face-to-face treatments were offered. The treatment centre was part of the Karolinska University Hospital, managed by the Stockholm County Council, and operated as a conventional psychiatric outpatient clinic. The majority of those seeking treatment were self-referrals, but could also be referred by their general practitioner. In either case, all patients had to complete an online screening battery of self-report measures after which they were invited to the clinic to undergo a structured face-to-face diagnostic interview conducted by a psychiatrist or a resident physicians. For those

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

7.

76 who were offered ICBT, treatment would typically be initiated within 48 hours. The duration
77 of the active psychotherapeutic intervention was twelve weeks, during which patients were
78 guided online by licensed psychologists who had training in CBT. After treatment, patients
79 were invited to the clinic for a post-treatment face-to-face follow-up visit; those who showed
80 insufficient improvement could therefore be referred elsewhere for additional treatment.

81
82 The intervention was based on a manual developed by Andersson and colleagues with
83 previously documented effects [21 22] and followed a protocol initially developed for
84 individual therapy of SAD [23]. When delivered as an internet-based intervention within the
85 context of routine psychiatric care, it has been shown to be non-inferior to conventional CBT
86 [13]. The content of the treatment was accessible in the form of web-based text modules
87 (similar to chapters in a self-help treatment manual) which were administered in a sequential
88 manner. As therapists regularly provided feedback on homework associated with each
89 module, they could monitor each patient's progress and provide individual support throughout
90 treatment. In addition, there were weekly online self-assessments of both social anxiety and
91 depressive symptoms.

92
93 Patients who had been discharged between October 2010 and June 2013 were informed of the
94 study and invited to complete a long-term follow-up assessment battery online, which have
95 previously been documented as a valid administration format. [24] In total, the study
96 comprised four measurement occasions: (1) pre-treatment, (2) post-treatment, (3) six-month-
97 follow-up and (4) long-term follow-up spanning a period of approximately one to four years
98 after treatment. The study, including its consent procedure, was approved by the Regional
99 Ethical Review Board in Stockholm, Sweden (no 2011/2091-31/3).

101 Outcome measures

102 *Social anxiety*

103 The self-report version of the Liebowitz Social Anxiety Scale (LSAS-SR) [25] was used as
104 the primary outcome measure. The LSAS-SR is a 24 item scale measuring both fear and
105 avoidance in performance and social situations as separate subscales. The instrument has a
106 high level of internal consistency (Cronbach's alpha = .95) as well as a high 12-week test-
107 retest reliability ($r = .83$) [25 26]. At baseline, the LSAS-SR alpha for the present sample was
108 .95. The LSAS-SR has showed strong convergent validity with other common self-report
109 measures of social anxiety such as the Social Interaction Anxiety Scale (SIAS) and the Social
110 Phobia Scale (SPS) [27] with correlation coefficients of 0.71 and 0.61 respectively [28]. A
111 cut-off score of 30 or less on the LSAS-SR has been suggested as indicative of probable
112 absence from social anxiety disorder [29]. Therefore, $LSAS-SR \leq 30$ was used as a threshold
113 value for calculating the remission rate throughout the study.

115 *Comorbid depression*

116 The Montgomery Åsberg Depression Rating Scale Self-Rated [30] (MADRS-S) was used to
117 assess change in depressive symptoms as a secondary outcome measure. MADRS-S measures
118 nine clinical characteristics of depression with a total score range of 0 to 54. The test-retest
119 reliability of MADRS-S has been shown to be high ($r = .80-.94$) [30]. Cronbach's alpha for
120 the sample at baseline was .87. A cut-off score of 13 or higher has been used to distinguish
121 depressed from non-depressed patients [31]. The MADRS-S has been shown to have a high
122 correlation with the commonly used Beck Depression Inventory (BDI) ($r = .87$) [32].

124 *Health-related quality of life*

Quality of life was evaluated using the EuroQol (EQ-5D).[33] Five health domains were assessed: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D has demonstrated acceptable psychometric properties and good construct validity.[34]

Potential prognostic variables

Baseline illness severity was rated by clinicians on a 7-point scale with the Clinical Global Impression – Severity Scale (CGI-S).[35] A treatment credibility scale, originally proposed by Borkovec and Nau [36], assessed patients’ level of confidence in the treatment. This was operationalized as the total score (0-50) of five items (e.g. “How much improvement do you expect from this treatment?”) measured on a continuous VAS from 0 to 10 (0 = no improvement at all to 10 = completely recovered/free from symptoms) after the first week of the treatment. Treatment adherence was defined as the number of modules that the patient had been able to work with during therapy as part of the treatment program, and such measured at post-treatment. Finally, having a family history of social anxiety was coded as a categorical variable during the diagnostic interview conducted by a clinician prior to treatment.

Adverse Events

Data on adverse events were collected at follow-up in order to identify whether ICBT might have provided any short- or long-term side effects. An adverse event was operationalized as any negative experience that a patient subjectively attributed to the ICBT intervention. Therefore, patients were asked to report these events as part of the online assessment battery, and were provided with an option to describe these in free text. Also, they were asked to rate the degree (on a four-point Likert scale) of which these adverse events affected their well-being (a) when they occurred and (b) to what degree they still affected their well-being.

150 Statistical analyses

151 Symptomatic change was analysed using longitudinal multilevel modelling. This approach
152 has the benefit of taking into account the hierarchical nature of repeated measurements (i.e.
153 the dependency of observations of outcome scores clustered within each patient who provided
154 repeated data). Two separate multilevel models were estimated: (i) a longitudinal growth
155 model investigating the overall symptomatic change over time, and (ii) a longitudinal growth
156 model investigating individual differences in the rate of change (i.e. the effect of potential
157 prognostic variables). In both models, a first-order autoregressive covariance structure for the
158 repeated measurements level was used as recommended in longitudinal studies where
159 correlations between measurements tend to weaken as time between them increases [37]. Two
160 approaches to treating time were considered; (a) either using a two-piece model with discrete
161 time, grouping measurements into four measurement occasions (i.e. pre-treatment, post-
162 treatment, 6-month-follow-up and long-term follow-up) or (b) a model with a continuous time
163 variable using the number of days to follow-up. Since grouping measurements facilitates the
164 interpretation of the model, this approach was used. However, due to the relatively wide
165 distribution of duration to long-term follow-up assessment (i.e. between 1-4 years), we tested
166 whether those who completed the long-term follow up at a short duration differed from those
167 who completed the follow up after a longer period in terms of the number of patients in
168 remission at the time of follow-up. For this purpose, patients were categorized into two
169 groups ("short" or "long" duration), operationalised as either 1 SD below or above the mean
170 duration, and analysed with a Chi-square design. Further, since the aim of this study was to
171 understand the sustainability of effects after completing treatment, a piecewise treatment of
172 time was conducted. By using a piecewise growth model, two growth curves may be fitted in
173 the same model, where each curve represents each developmental stage in the study (i.e.
174 treatment phase and follow-up phase). Piece 1 (T_1) therefore constituted the phase between

pre- and post-treatment and piece 2 (T_2) spanned the period between post-treatment, 6-month-follow-up and long-term follow-up. For the T_1 time variable, the four measurement occasions were coded as 0 1 1 1, and for the T_2 time variable, measurement occasions were coded as 0 0 1 2. The benefit of this approach was the possibility to test whether there was a significant linear trend of continued improvement or worsening of symptoms after having completed treatment. The multilevel model testing the effect of outcome predictors included simultaneous entry of the following measurements: baseline CGI-S, level of adherence, treatment credibility and presence of family history of social anxiety. Consequently, the effect of each prognostic factor was estimated while controlling for the effects of the others. Predictor variables were standardized prior to analysis to facilitate comparison between effects measured on different scales. Within-group Cohen's d effect sizes for mean differences were calculated using estimated means and observed standard deviations and correlations between the repeated measurements.

Missing Data Analysis

Multilevel modelling provides several benefits in the treatment of missing data. As opposed to traditional complete case analyses where cases having incomplete data are deleted from the analysis, multilevel models incorporate all available data. Therefore, all patients who provided at least one outcome measurement were included in the analyses. All models were fitted using maximum likelihood estimation which calculates estimates of the statistical parameters most likely to have produced the observed data.[38] In order to investigate any relationship between post-measurements and missing data at long-term follow-up, an independent-samples t-test was performed comparing mean post-treatment LSAS-SR among those who provided long-term follow-up data with those who were lost to long-term follow-up.

RESULTS

Sample description

Patient characteristics are presented in Table 1. The sample comprised 446 subjects. Follow-up assessments were completed between 1.2 to 4.1 years from baseline ($M = 2.66$, $SD = 0.80$).

Table 1. *Description of the participants.*

Variable		
Gender	Women	54.9%
	Men	45.1%
Age	Mean age (SD)	32.67 (9.71)
	Min-max	18-63
Education ^a	7-9 years in school	1.9
	Incomplete vocational or secondary school	4.9
	Vocational school	3.0
	Secondary school	24.5
	University. started but not completed studies	23.1
	University. completed studies	42.5
Marital status	Married or de facto	54.5%
Parental status	Parent (yes)	33%
Social anxiety (pre-treatment)	LSAS clinician rated	66.56 (22.59)
	LSAS self-rated	69.27 (23.23)
Treatment adherence	Mean number of activated modules (SD)	8 (3.35)
Treatment Credibility Scale	Mean score on Treatment Credibility Scale (SD)	36.24 (7.53)
Time since debut of first SAD symptoms, years (SD)		15.93 (10.64)
Global functioning	GAF-score (SD)	61.65 (7.29)
CGI-S Global Severity	Mean CGI-S score (SD)	3.79 (0.83)
	Normal. not at all ill	0%
	Borderline mentally ill	4%
	Mildly ill	35%
	Moderately ill	41%
	Markedly ill	19%
	Severely ill	1%
	Extremely ill	0%

Co-morbid depression	MADRS clinician rated (SD)	15.21 (8.00)
	MADRS-S self-rated (SD)	14.56 (7.75)
Currently on psychotropic medication for SAD		180 (46.8%)
Change of medication after ICBT	No change. Neither during ICBT or after	189 (58.9%)
	No change. Had medication during ICBT. and still do	51 (15.9%)
	Yes. Medication during ICBT but not now	27 (8.4%)
	Yes. No medication during ICBT. but currently on medication	54 (16.8%)
Other psychological treatment after ICBT	No	254 (79.1%)
	Cognitive behavioural therapy (CBT)	47 (14.6%)
	Psychodynamic therapy	6 (1.9%)
	Other structured psychological therapy	14 (4.4%)
Days to follow-up	Mean (SD)	971 (293)
	Minimum	441
	Maximum	1492
	25 th percentile	683
	50 th percentile	1006
	75 th percentile	1240

Note: Total N = 446. SAD, social anxiety disorder. CBT, Cognitive Behaviour Therapy. ICBT, Internet-based Cognitive Behaviour Therapy. CGI-S, The Clinical Global Impression - Severity scale. SD, standard deviation. LSAS-SR; Liebowitz Social Anxiety Disorder Scale - self-rated. MADRS-S; Montgomery–Asberg Depression Rating Scale score - self-rated.

^a Level of education was rated on a 7-point scale (1= less than 7-9 years in school; 2 = 7-9 years in school; 3 = incomplete vocational or secondary school; 4 = vocational school; 5 = secondary school; 6 = university, started but not completed studies; 7 = completed university studies).

Attrition and adherence

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

14.

Of 446 patients who provided baseline measurements, 391 (88%) provided post-treatment data, 173 (39%) patients provided six-month follow-up data and 321 (72%) provided long-term follow-up data on the main outcome measure. The mean level of treatment adherence was 8 (SD = 3.35) of 12 modules activated.

Remission

At post-treatment, 20.7% of patients who provided data had achieved remission from SAD, 34.1% at six-month follow-up and 35.2% at the time of long-term follow-up. Remission rate at long-term follow-up was found to be independent of when the follow-up assessment was completed; χ^2 (1, N = 141) = 1.20, p = .27. However, there was a significant difference in the proportion of patients in remission at follow-up depending on the use of psychotropic medication; χ^2 (2, N = 267) = 12.41, p < .01, indicating a moderate association (Cramer's V = 0.22, p < .02). Among those who reported no use of medication either during treatment or at the time of long-term follow up, 41.8% (79 patients out of 189) had achieved remission, as opposed to 15.7% (8 out of 51) among those who reported using medication during treatment and at the time of long-term follow up.

Multilevel models of long-term symptomatic improvement

Piecewise growth models that included a random intercept, a random linear slope for the treatment phase (piece 1) and a fixed linear slope for the post-treatment to long-term follow-up phase (piece 2) were estimated for LSAS-SR, MADRS-S and EQ-5D. Model-implied means and mean differences and observed standard deviations are presented together with associated effect sizes in Table 2.

Table 2. Estimated parameters from growth curve analysis of continuous outcomes.

Measure	Pre	Post	6MFU	LFU	Effect sizes (Cohen's <i>d</i>) with 95% CI			Rate of change	
	M (SD)	M (SD)	M (SD)	M (SD)	Pre to Post	Pre to 6MFU	Pre to LFU	Pre to Post	Post to LFU
								β 95% CI	β 95% CI
LSAS-SR	69.07 (22.90)	50.38 (24.37)	46.13 (26.21)	41.87 (24.24)	0.79 [0.69, 0.89]	0.92 [0.75, 1.09]	1.17 [1.02, 1.32]	-18.69*** [-20.63,-16.74]	-4.26*** [-5.33,-3.09]
MADRS-S	14.57 (7.62)	9.78 (8.03)	9.63 (9.11)	9.48 (7.97)	0.61 [0.52, 0.70]	0.59 [0.42, 0.75]	0.67 [0.54, 0.80]	-4.78*** [-5.45,-4.12]	-0.15 [-0.59,-0.28]
EQ-5D	0.81 (0.13)	0.82 (0.15)	0.83 (0.18)	0.85 (0.18)	-0.12 [-0.22, 0.01]	-0.17 [-0.36, 0.02]	-0.25 [-0.40, -0.10]	0.02* [0.00, 0.03]	0.01* [0.00, 0.02]

Note. Observed means and standard deviations for pre-treatment, and estimated means and observed standard deviations for post-treatment, six-month-follow-up and long-term follow-up are reported. For Cohen's *d*, an effect size of 0.2 is considered to be a small effect, 0.5 a medium effect and > 0.8 a large effect. For slope coefficients of rate of change, significant effects of time on outcome is denoted as ***, *p* < .001; **, *p* < .01 and *, *p* < .05. M, mean; SD, standard deviation; Pre, before treatment; Post, post-treatment; 6MFU, 6 months after treatment; LFU, long-term follow-up 1.2 to 4 years after treatment start; CI, confidence interval; LSAS-SR, Liebowitz Social Anxiety Scale questionnaire-Self-report; MADRS-S, Montgomery Åsberg Depression Rating Scale-Self-report; EQ-5D, Health-Related Quality of Life.

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

16.

There was a significant effect of linear time on all three outcome measures between pre-treatment and post-treatment (piece 1), reflecting large improvements in symptoms of social anxiety, moderate improvements in symptoms of depression and small improvements in health-related quality of life during the active treatment phase. After treatment (piece 2), continued long-term improvements (i.e. a significant effect of time) in symptoms of social anxiety and quality of life were observed. Also, achieved improvements in symptoms of depression were maintained (i.e. a non-significant effect of time).

Adverse Effects

Of 281 patients that provided data on adverse effects, 22 (7.8%) subjects reported having experienced at least one adverse effect attributed to ICBT. However, 251 (89.3%) subjects responded that regardless of whether or not they had experienced any adverse effect, these were in such cases minor and had no significant effect on them during treatment and 263 (93.6%) reported that they experienced no significant adverse long-term effects. Nine (3.2%) subjects reported that adverse events attributed to the intervention had a very negative acute effect and three (1.1%) reported that these had also very negative long-term effects. Common side-effects described by subjects were experiencing feelings of inadequacy, guilt, stress, worry or failure of not adhering to the treatment schedule (sometimes triggered by receiving well-intended reminders from therapists), anxiety associated with exposure assignments and anxiety associated with an increased self-awareness of symptoms, negative cognitions and maladaptive behaviours.

Multilevel model explaining individual differences in the rate of symptomatic change

Estimates of model parameters predicting individual differences in long-term rate of change in symptoms of social anxiety are presented in Table 3 and illustrated in Figures 4 and 5. A

higher level of illness severity (i.e. baseline CGI-S scores) was associated with a faster rate of improvement, whereas having a family history of social anxiety was related to a slower rate of improvement. When CGI-S scores and family history of social anxiety were controlled for, adherence and treatment credibility had no significant predictive value in explaining individual differences in the long-term rate of change.

Table 3. Estimated parameters from growth curve analysis examining the long-term effects of adherence, treatment credibility, illness severity and family history on the rate of symptomatic improvement.

Variables	Estimate	Standard Error	<i>p</i>	95% Confidence Interval	
				Lower Bound	Upper Bound
Intercept	68.47	1.13	***	66.25	70.69
Time	-27.48	1.51	***	-30.45	-24.50
Predictors					
Time × Adherence	-2.29	1.75		-5.73	1.15
Time × Treatment credibility	-2.36	1.57		-5.46	0.74
Time × CGI-S	-6.03	1.53	***	-9.05	-3.01
Time × Family history of social anxiety	3.40	1.45	*	0.55	6.26

Note. *, *p* < 0.05. ***, *p* < 0.001. SE; standard error. Dependent Variable is LSAS-SR.

Predictor variables were standardized prior to analysis to facilitate comparison between effects measured on different scales. Predictor coefficients reflect the effect on the rate of change in social anxiety over the entire study period (from pre-treatment to long-term follow-up). LSAS-SR; Liebowitz Social Anxiety Disorder Scale - self-rated. CGI-S; The Clinical Global Impression - Severity scale. Adherence was operationalized as the number of activated treatment modules.

Missing Data Analysis

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

18.

To test any association between the level of social anxiety at post-treatment and missing data at long-term follow-up, an independent-samples t-test was performed comparing mean post-treatment LSAS-SR scores among those who provided long-term follow-up data with those who were lost to follow-up. There was no difference in post-treatment LSAS-SR scores between patients who provided follow-up data ($M = 49.08$, $SD = 23.68$) and those who were lost to follow-up ($M = 52.64$, $SD = 26.30$); $t(389) = -1.247$, $p = 0.213$. Also, there was no difference in pre-treatment LSAS-SR scores between patients who provided follow-up data ($M = 69.07$, $SD = 22.23$) and those who were lost to follow-up ($M = 69.18$, $SD = 25.99$); $t(444) = -0.046$, $p = 0.964$.

DISCUSSION

Previous research on the clinical effectiveness of ICBT for SAD has demonstrated large short-term effects [12 13]. The aim of the present study was to determine the sustainability of treatment effects in a naturalistic setting (i.e. routine psychiatric care) and identify factors that might explain individual differences in long-term rate of improvement. We are only aware of three long-term follow-up studies on ICBT for SAD, all of which were clinical trials. In these, large effect sizes were observed after treatment and sustained at 2.5-year follow-up [9], at four-year follow-up [11] and at five-year follow-up [10]. In line with these reports, we have observed similar results in the present study within a naturalistic clinical context; a large treatment effect achieved at post-treatment and that patients, overall, continued to improve in symptoms of social anxiety between 1-4 years after treatment. In addition, continued improvements in health-related quality of life were observed during the follow-up period.

A secondary aim of this study was to identify prognostic patient characteristics that moderate long-term treatment response. Expanding our knowledge about which patients are more

likely to benefit from – or fail to respond to – ICBT might help further refining inclusion guidelines and modifying treatment strategies to better suit different patient needs. Although adherence and treatment credibility has been associated with better outcome in previous research [19], we have found that these factors lack predictive value over longer follow-up timeframes when illness severity is controlled for. Evidence regarding the prognostic value of baseline illness severity is somewhat inconclusive. For example, one review [39] on outcome predictors of conventional CBT for SAD found that although higher baseline severity predicted higher levels of severity after treatment, it was not related to the degree of improvement, whereas another review [40] concluded that greater illness severity predicted a worse response. Consequently, our finding that illness severity is associated with a faster rate of symptomatic improvement is surprising. Nonetheless, this observation is a strong indicator that ICBT is also effective for patients who are severely ill, which may be contrary to common beliefs regarding internet-delivered therapies. We also identified family history of social anxiety as a predictor of poorer outcome. This relationship has been observed in both pharmacological treatment for SAD [41] and in an RCT on ICBT for SAD [17]. Although family history has been shown to be associated with a two- to three-fold risk for developing SAD [42], it is unclear which mediating mechanisms of genetic and environmental factors might be responsible for the variance in treatment effects. Still, the identification of family history as a long-term outcome predictor may have implications for the need to monitor this patient group more carefully due to an increased risk of a lower response rate and possibly also a higher level of therapist guidance during exposure training.

Finally, although we observed a difference in proportions of patients in remission from SAD at follow-up depending on the use of medication during and after treatment (41.8% of patients with no medication during or after ICBT had achieved remission at follow-up as

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

20.

opposed to only 15.7% among those who reported using medication during treatment and at the time of follow-up), these subgroups of patients may be difficult to compare because we do not know how they differ in terms of illness history.

There are some limitations of the study, the most apparent being the lack of a comparison group to control for spontaneous recovery. As this was a cohort study conducted within a naturalistic setting, this was an unavoidable limitation. However, available empirical data suggest a low probability of spontaneous recovery from SAD. For example, an eight-year study following the long-term course of SAD reported that only 13-14% had achieved remission after one year [43], which can be compared to 34.1% at six-month follow-up in the present study. Also, ICBT for SAD has demonstrated superiority to waiting list controls [6 22 44-47]. Taken together, it would seem unlikely that the observed improvements among patients in the present study might be attributed to the effect of time alone. A second limitation concerns the operational definition of treatment adherence. This partly concerns defining adherence as the number of activated modules. Since participation and adherence in CBT typically refer to both in-session and out of session behaviour, homework assignments reflect a critical aspect of the treatment package. Therefore, since each new module was activated only after completion of the previous one, it is possible that many patients did not fully complete the homework assignment related to their last module. However, although the degree of completion of the last activated module is unclear, we still know how many modules each patient worked with at a minimum (i.e. all until the last activated module). Consequently, for some patients (those who did not complete the last module they had access to) the level of adherence may be overrated by 1. On the other hand, a more serious potential risk of measurement error in regard to measuring adherence is the lack of information regarding how closely the number of modules correlates with actual therapeutic activity.

Third, a note on the statistical approach of handling the relatively wide time-frame of the long-term follow-up “time point” is warranted, since these de facto ranges over a period of several years. As described in the methods section, there were mainly two alternative approaches to model how the outcome variables evolve over time. We could either treat time as discrete or continuous. Within a discrete framework, time values are defined as distinct time periods or measurement occasions; in the present study, pre-treatment, post-treatment, 6-month-follow-up and long-term follow-up measurements were categorised into four separate assessment occasions irrespective of the actual duration since baseline. The alternative approach, treating time as continuous, would have meant that the time variable would range over the complete duration of the study (i.e. 1492 days). We acknowledge that there are benefits with both approaches. For example, it could be argued that developing a model using a continuous time variable might be more exact and mathematically tractable. On the other hand, it might be easier to understand and interpret a model that corresponds to how the theoretical hypothesis to be tested is expressed (e.g. to understand the degree of symptomatic improvement at long-term follow-up). Ultimately, we chose a discrete time framework in order to facilitate the development and interpretation of the multilevel model.

In sum, this study demonstrates that ICBT for the treatment of SAD in regular clinical practice is effective not only short-term but also long-term. Patients also reported significant reductions in co-morbid depressive symptoms and improved quality of life. Furthermore, higher illness severity was related to a greater rate of symptomatic improvement, whereas having a family history of social anxiety was associated with worse response. Considering that SAD is one of the most common anxiety disorders and that access to CBT is rather limited, ICBT could significantly increase the availability of evidence-based effective treatments for a large patient group.

COMPETING INTERESTS

All authors declare no competing interests.

FUNDING

This study was supported by research grants from Stockholm County Council. It is a public institution and had no role in study design, data collection, analysis, data interpretation, manuscript writing, or decision to submit for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

REFERENCES

1. Ruscio AM, Brown TA, Chiu WT, et al. Social fears and social phobia in the USA: results from the National Comorbidity Survey Replication. *Psychol Med* 2008;**38**(01):15-28 doi: doi:10.1017/S0033291707001699[published Online First: Epub Date]].
2. Reich J, Goldenberg I, Vasile R, et al. A prospective follow-along study of the course of social phobia. *Psychiatry Res* 1994;**54**(3):249-58
3. Stein MB, Roy-Byrne PP, Craske MG, et al. Functional impact and health utility of anxiety disorders in primary care outpatients. *Medical care* 2005;**43**(12):1164-70
4. Hofmann SG. Cognitive factors that maintain social anxiety disorder: a comprehensive model and its treatment implications. *Cognitive behaviour therapy* 2007;**36**(4):193-209 doi: 10.1080/16506070701421313[published Online First: Epub Date]].
5. Mewton L, Smith J, Rossouw P, et al. Current perspectives on Internet-delivered cognitive behavioral therapy for adults with anxiety and related disorders. *Psychology research and behavior management* 2014;**7**:37-46 doi: 10.2147/PRBM.S40879[published Online First: Epub Date]].

6. Furmark T, Carlbring P, Hedman E, et al. Guided and unguided self-help for social anxiety disorder: randomised controlled trial. *The British journal of psychiatry : the journal of mental science* 2009;**195**(5):440-7 doi: 10.1192/bjp.bp.108.060996[published Online First: Epub Date]].

7. Andersson G, Cuijpers P, Carlbring P, et al. Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis. *World psychiatry : official journal of the World Psychiatric Association* 2014;**13**(3):288-95 doi: 10.1002/wps.20151[published Online First: Epub Date]].

8. Boettcher J, Carlbring P, Renneberg B, et al. Internet-Based Interventions for Social Anxiety Disorder - an Overview. *Verhaltenstherapie* 2013;**23**(3):160-68 doi: Doi 10.1159/000354747[published Online First: Epub Date]].

9. Carlbring P, Nordgren LB, Furmark T, et al. Long-term outcome of Internet-delivered cognitive-behavioural therapy for social phobia: a 30-month follow-up. *Behaviour research and therapy* 2009;**47**(10):848-50 doi: 10.1016/j.brat.2009.06.012[published Online First: Epub Date]].

10. Hedman E, Furmark T, Carlbring P, et al. A 5-Year follow-up of internet-based cognitive behavior therapy for social anxiety disorder. *J Med Internet Res* 2011;**13**(2):e39 doi: 10.2196/jmir.1776[published Online First: Epub Date]].

11. Hedman E, El Alaoui S, Lindefors N, et al. Clinical effectiveness and cost-effectiveness of Internet- vs. group-based cognitive behavior therapy for social anxiety disorder: 4-Year follow-up of a randomized trial. *Behaviour research and therapy* 2014;**59C**:20-29 doi: 10.1016/j.brat.2014.05.010[published Online First: Epub Date]].

12. Aydos L, Titov N, Andrews G. Shyness 5: the clinical effectiveness of Internet-based clinician-assisted treatment of social phobia. *Australasian psychiatry : bulletin of*

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

24.

- Royal Australian and New Zealand College of Psychiatrists 2009;**17**(6):488-92 doi:
10.1080/10398560903284943[published Online First: Epub Date]].
13. Hedman E, Andersson G, Ljotsson B, et al. Internet-based cognitive behavior therapy vs. cognitive behavioral group therapy for social anxiety disorder: a randomized controlled non-inferiority trial. *PloS one* 2011;**6**(3):e18001 doi:
10.1371/journal.pone.0018001[published Online First: Epub Date]].
14. El Alaoui S, Hedman E, Kaldo V, et al. Effectiveness of Internet-based Cognitive Behavior Therapy for Social Anxiety Disorder in Clinical Psychiatry. *Journal of consulting and clinical psychology* 2015(In press)
15. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical-Evidence of Bias - Dimensions of Methodological Quality Associated with Estimates of Treatment Effects in Controlled Trials. *Jama-J Am Med Assoc* 1995;**273**(5):408-12 doi: DOI
10.1001/jama.273.5.408[published Online First: Epub Date]].
16. McEvoy PM, Nathan P, Rapee RM, et al. Cognitive behavioural group therapy for social phobia: evidence of transportability to community clinics. *Behaviour research and therapy* 2012;**50**(4):258-65 doi: 10.1016/j.brat.2012.01.009[published Online First: Epub Date]].
17. Hedman E, Andersson E, Ljotsson B, et al. Clinical and genetic outcome determinants of internet- and group-based cognitive behavior therapy for social anxiety disorder. *Acta psychiatrica Scandinavica* 2012;**126**(2):126-36 doi: 10.1111/j.1600-0447.2012.01834.x[published Online First: Epub Date]].
18. Scholing A, Emmelkamp PM. Prediction of treatment outcome in social phobia: a cross-validation. *Behaviour research and therapy* 1999;**37**(7):659-70

19. Nordgreen T, Havik OE, Ost LG, et al. Outcome predictors in guided and unguided self-help for social anxiety disorder. *Behaviour research and therapy* 2012;**50**(1):13-21 doi: 10.1016/j.brat.2011.10.009[published Online First: Epub Date]].

20. El Alaoui S, Hedman E, Ljótsson B, et al. Predictors of Outcome and Adherence in Internet-based Cognitive Behavior Therapy for Social Anxiety Disorder in Routine Psychiatric Care. Unpublished manuscript

21. Furmark T, Carlbring P, Hedman E, et al. Guided and unguided self-help for social anxiety disorder: randomised controlled trial. *Brit J Psychiat* 2009;**195**(5):440-7 doi: 10.1192/bjp.bp.108.060996[published Online First: Epub Date]].

22. Andersson G, Carlbring P, Holmstrom A, et al. Internet-based self-help with therapist feedback and in vivo group exposure for social phobia: a randomized controlled trial. *Journal of consulting and clinical psychology* 2006;**74**(4):677-86 doi: 10.1037/0022-006X.74.4.677[published Online First: Epub Date]].

23. Clark DM, Wells A. A cognitive model of social phobia. In: HEIMBERG RG, LEIBOWITZ M, HOPE DA, et al., eds. *Social phobia: Diagnosis, assessment and treatment*. New York: Guilford press, 1995.

24. Hedman E, Ljótsson B, Rück C, et al. 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

25. Baker SL, Heinrichs N, Kim H-J, et al. The Liebowitz Social Anxiety Scale as a self-report instrument: a preliminary psychometric analysis. *Behav Res Ther* 2002;**40**(6):701-15

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

26.

26. Heimberg RG, Horner KJ, Juster HR, et al. Psychometric properties of the Liebowitz Social Anxiety Scale. *Psychol Med* 1999;**29**(01):199-212 doi: doi:10.1017/S0033291798007879[published Online First: Epub Date]].
27. Mattick RP, Clarke JC. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. *Behaviour research and therapy* 1998;**36**(4):455-70
28. Fresco DM, Coles ME, Heimberg RG, et al. The Liebowitz Social Anxiety Scale: a comparison of the psychometric properties of self-report and clinician-administered formats. *Psychol Med* 2001;**31**(6):1025-35
29. Rytwinski NK, Fresco DM, Heimberg RG, et al. Screening for Social Anxiety Disorder with the Self-Report Version of the Liebowitz Social Anxiety Scale. *Depression and anxiety* 2009;**26**(1):34-38 doi: Doi 10.1002/Da.20503[published Online First: Epub Date]].
30. Svanborg P, Asberg M. A new self-rating scale for depression and anxiety states based on the Comprehensive Psychopathological Rating Scale. *Acta psychiatrica Scandinavica* 1994;**89**(1):21-8
31. Svanborg P, Ekselius L. Self-assessment of DSM-IV criteria for major depression in psychiatric out- and inpatients. *Nordic journal of psychiatry* 2003;**57**(4):291-6
32. Svanborg P, Asberg M. A comparison between the Beck Depression Inventory (BDI) and the self-rating version of the Montgomery Asberg Depression Rating Scale (MADRS). *J Affect Disorders* 2001;**64**(2-3):203-16 doi: Doi 10.1016/S0165-0327(00)00242-1[published Online First: Epub Date]].
33. EuroQol-Group. EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy* 1990;**16**(3):199-208

34. Stark RG, Reitmeir P, Leidl R, et al. Validity, reliability, and responsiveness of the EQ-5D in inflammatory bowel disease in Germany. *Inflamm Bowel Dis* 2010;**16**(1):42-51 doi: 10.1002/ibd.20989[published Online First: Epub Date]].

35. Guy W. Clinical Global Impressions. ECDEU Manual. Rockville, MD: NIMH: US Dept of Health and Human Services, 1976:217-22.

36. Borkovec TD, Nau SD. Credibility of analogue therapy rationales. *Journal of behavior therapy and experimental psychiatry* 1972;**3**(4):257-60

37. Heck RH, Thomas SL, Tabata LN. *Multilevel and longitudinal modeling with IBM SPSS*. Second edition. ed. New York, NY: Routledge, 2013.

38. Hox JJ. *Multilevel analysis : techniques and applications*. 2nd ed. New York: Routledge, 2010.

39. 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. *Nordic journal of psychiatry* 2010;**64**(2):94-105 doi: 10.3109/08039480903426929[published Online First: Epub Date]].

40. Mululo SC, Menezes GB, Vigne P, et al. A review on predictors of treatment outcome in social anxiety disorder. *Revista brasileira de psiquiatria* 2012;**34**(1):92-100

41. Slaap BR, van Vliet IM, Westenberg HG, et al. Responders and non-responders to drug treatment in social phobia: differences at baseline and prediction of response. *J Affect Disord* 1996;**39**(1):13-9

42. Tillfors M, Furmark T, Ekselius L, et al. Social phobia and avoidant personality disorder as related to parental history of social anxiety: a general population study. *Behaviour research and therapy* 2001;**39**(3):289-98

LONG-TERM EFFECTIVENESS OF INTERNET-BASED CBT

28.

43. 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**(5):637-43
44. Titov N, Andrews G, Choi I, et al. Shyness 3: randomized controlled trial of guided versus unguided Internet-based CBT for social phobia. *Aust Nz J Psychiat* 2008;**42**(12):1030-40 doi: Doi 10.1080/00048670802512107[published Online First: Epub Date]].
45. Titov N, Andrews G, Schwencke G. Shyness 2: treating social phobia online: replication and extension. *The Australian and New Zealand journal of psychiatry* 2008;**42**(7):595-605 doi: 10.1080/00048670802119820[published Online First: Epub Date]].
46. Titov N, Andrews G, Schwencke G, et al. Shyness 1: distance treatment of social phobia over the Internet. *The Australian and New Zealand journal of psychiatry* 2008;**42**(7):585-94 doi: 10.1080/00048670802119762[published Online First: Epub Date]].
47. Carlbring P, Gunnarsdottir M, Hedensjo L, et al. Treatment of social phobia: randomised trial of internet-delivered cognitive-behavioural therapy with telephone support. *The British journal of psychiatry : the journal of mental science* 2007;**190**:123-8 doi: 10.1192/bjp.bp.105.020107[published Online First: Epub Date]].

FIGURE LEGENDS

Figure 1. Improvement in social anxiety after internet-based cognitive behavioural therapy for social anxiety disorder. Means are estimated from a linear piecewise multilevel growth model, depicted with 95% confidence intervals. LSAS-SR, Liebowitz Social Anxiety Scale questionnaire-Self-report.

Figure 2. Improvement in co-morbid depressive symptoms after internet-based cognitive behavioural therapy for social anxiety disorder. Means are estimated from a linear piecewise multilevel growth model, depicted with 95% confidence intervals. MADRS-S, Montgomery Åsberg Depression Rating Scale-Self-report.

Figure 3. Improvement in health-related quality of life after internet-based cognitive behavioural therapy for social anxiety disorder. Means are estimated from a linear piecewise multilevel growth model, depicted with 95% confidence intervals. EQ-5D, Health-Related Quality of Life.

Figure 4. Predicted long-term symptomatic change based on individual differences in illness severity. Predicted trajectory of social anxiety symptoms after internet-based cognitive behavioural therapy for social anxiety disorder. For illustrative purposes, a categorization was performed to depict predicted growth curves for patients scoring high and low on the Clinical Global Impression - Severity scale. High severity was operationalized as 1 standard deviation above the mean CGI-S score and low credibility as 1 standard deviation below the mean. Mean CGI-S was 3.79 (SD = 0.83). LSAS-SR, Liebowitz Social Anxiety Scale questionnaire-Self-report; CGI-S; The Clinical Global Impression - Severity scale; SD, standard deviation.

Figure 5. Predicted long-term symptomatic change based on individual differences in family history of social anxiety. Predicted growth curves for patients reporting the having a family history of social anxiety. LSAS-SR, Liebowitz Social Anxiety Scale questionnaire-Self-report.

For peer review only

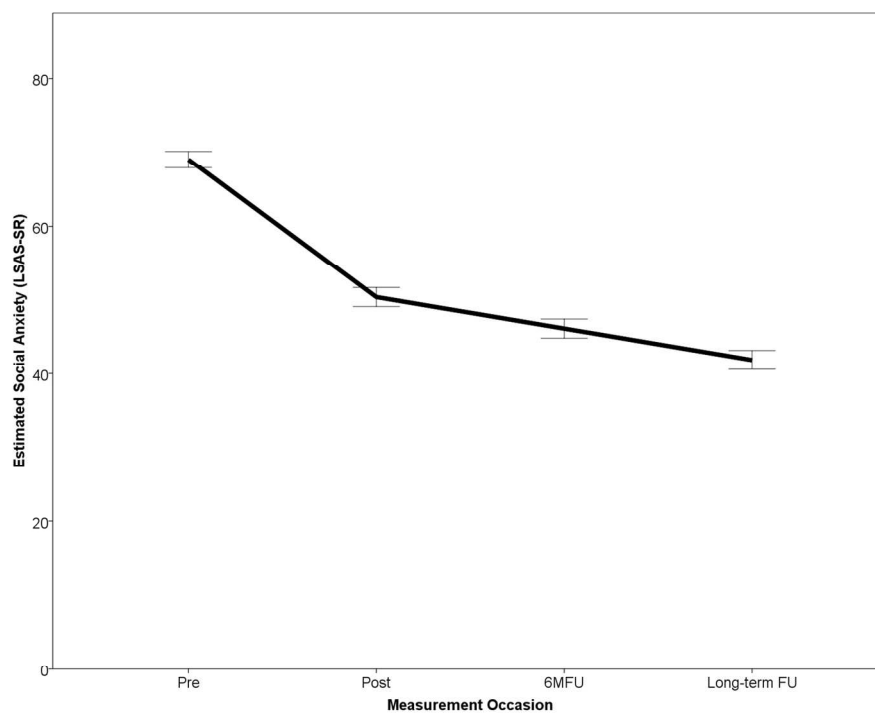


Figure 1. Improvement in social anxiety after internet-based cognitive behavioural therapy for social anxiety disorder.
150x150mm (300 x 300 DPI)

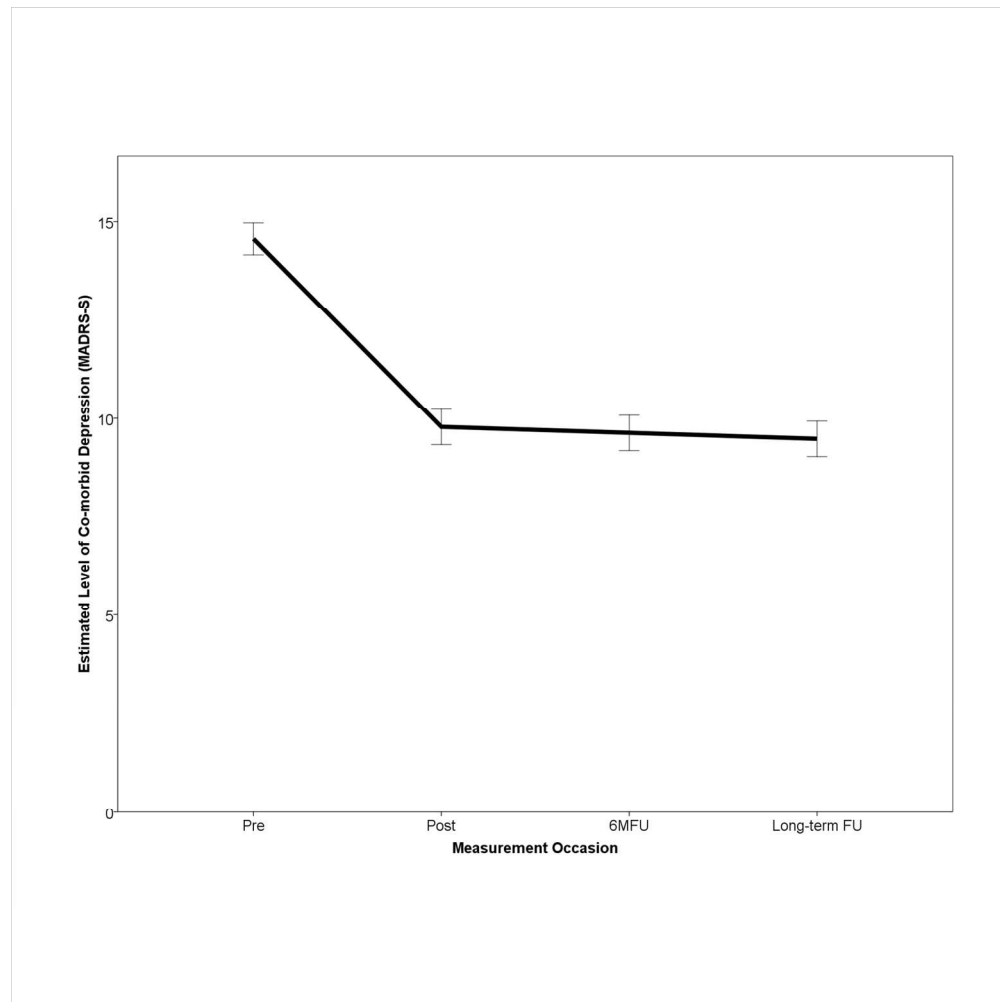


Figure 2. Improvement in co-morbid depressive symptoms after internet-based cognitive behavioural therapy for social anxiety disorder.
150x150mm (300 x 300 DPI)

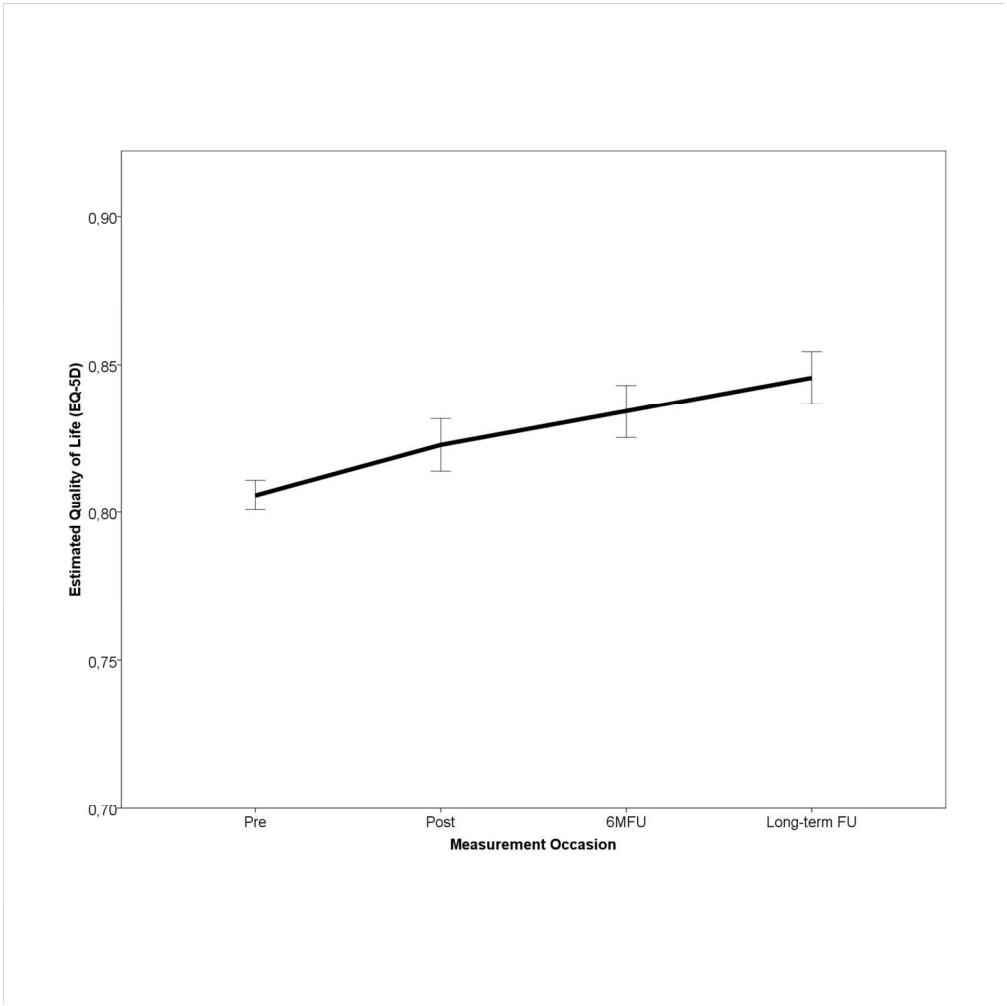


Figure 3. Improvement in health-related quality of life after internet-based cognitive behavioural therapy for social anxiety disorder.
150x150mm (300 x 300 DPI)

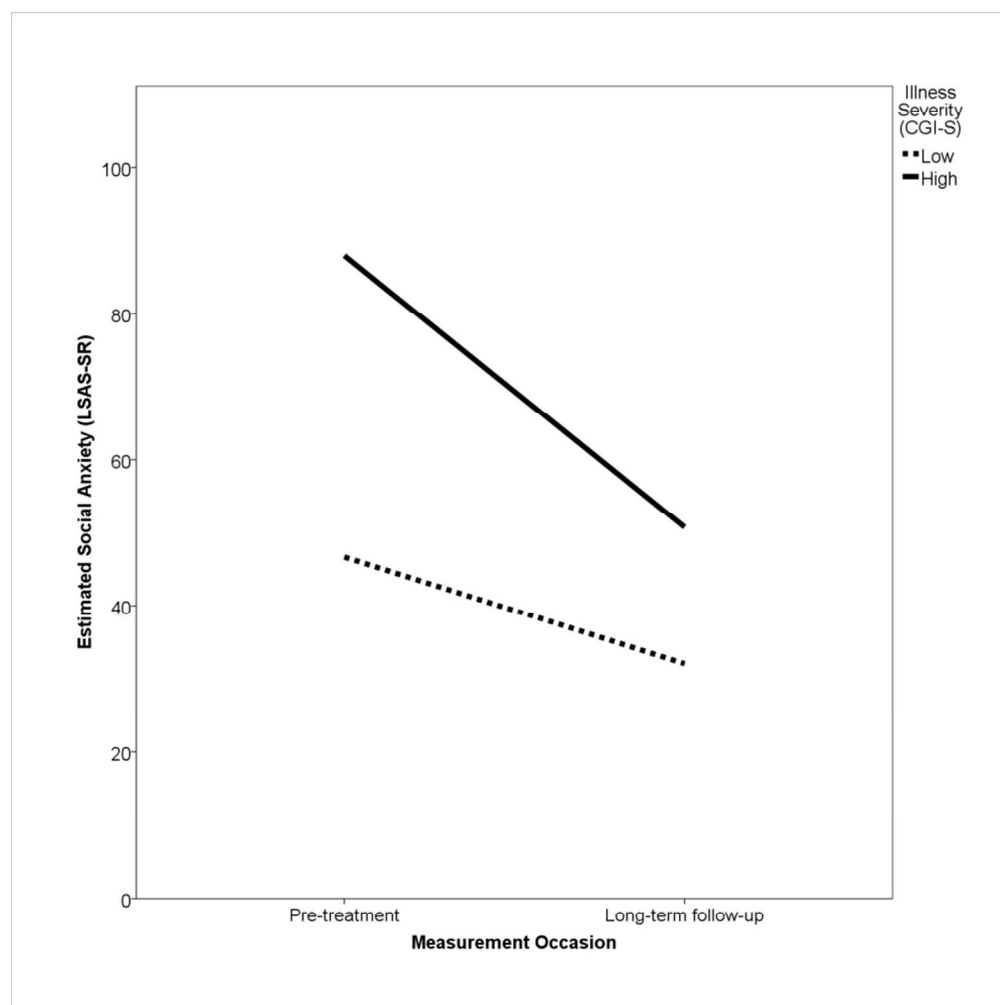


Figure 4. Predicted long-term symptomatic change based on individual differences in illness severity.
170x170mm (150 x 150 DPI)

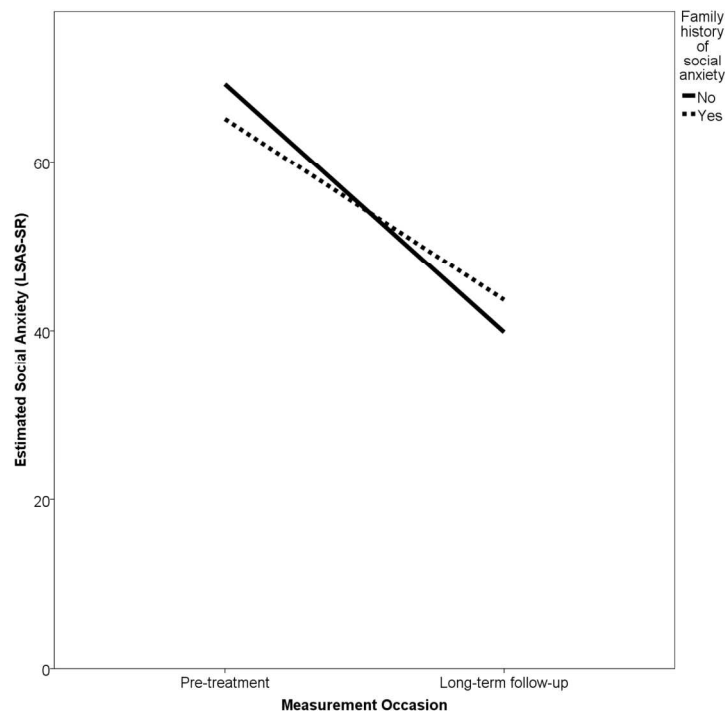


Figure 5. Predicted long-term symptomatic change based on individual differences in family history of social anxiety.
170x170mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.