From THE DEPARTMENT OF CLINICAL NEUROSCIENCE
Karolinska Institutet, Stockholm, Sweden

INTERNET-BASED TREATMENT FOR DEPRESSION AND PANIC DISORDER
From Development to Deployment

JAN BERGSTRÖM

Karolinska Institutet

Stockholm 2010

Published by Karolinska Institutet. Printed by Larserics Digital Print AB.

Cover illustration by Therése Wall.

ISBN 978-91-7409-800-6

Dedicated to all those who participated in these studies,
by courageously struggling with anxiety and depression.

ABSTRACT

Major depression (MD) and panic disorder (PD) are two common disorders for which evidence based psychological treatments such as cognitive behaviour therapy (CBT) have been developed. The accessibility of such treatment is however limited. The use of Internet-based CBT (self-help programmes accompanied by brief therapist support by e-mail) is a promising way to increase accessibility.

The first aim of this thesis was to investigate if Internet treatment was effective in reducing depressive symptoms and if it was possible to predict which participants would benefit from such treatment. The second aim of the thesis was to investigate if Internet treatment was effective for PD patients in a regular care setting, in comparison with traditional group-administered CBT, and in addition, to compare the cost-effectiveness of the two treatments.

In Study I 85 participants were randomised to either an Internet treatment or to an attention control condition (an online discussion group). Post-treatment measures of depression showed large effect sizes and improvements were sustained at a 6-month follow-up, thus showing that Internet treatment was effective in reducing mild to moderate symptoms of depression. Study II analysed predictors of treatment outcome at the 6-month follow-up of Study I. Higher self-reported severity at baseline was associated with poorer outcome and a negative correlation was found between number of previous episodes of depression and improvement in treatment.

Study III was an open effectiveness trial evaluating Internet treatment, which in previous studies had been shown to be effective with self-recruited participants, within a regular psychiatric setting for 20 PD patients referred for treatment. After treatment 75% of patients were considered to have responded to treatment, and at the 6-month follow-up this proportion was 70%, indicating that this treatment form was transferable to a regular care setting with sustained effectiveness.

Study IV was a randomised clinical trial comparing Internet- and group-administered CBT for PD with 104 patients in a psychiatric setting. Both treatments produced significant improvements, and there were no statistically significant differences between them at post-treatment or at the 6-month follow up. A cost-effectiveness analysis showed that the Internet treatment was more cost-effective than the group treatment with regard to therapist time.

This thesis provides evidence that Internet treatment is effective in reducing symptoms of depression and of PD. Internet treatment is as effective as traditionally administered group CBT in a regular care setting with PD patients referred for treatment. The thesis also provides evidence that Internet treatment for PD is more cost-effective than group treatment. Taken together, the results support the implementation of Internet treatment for depression and PD within regular health care settings.

Keywords: depression, panic disorder, agoraphobia, cognitive behaviour therapy, self-help, bibliotherapy, Internet, effectiveness, cost-effectiveness

RÉSUMÉ

La dépression majeure (DM) et le trouble panique (TP) sont deux troubles pour lesquels des traitements psychologiques efficaces ont été développés, comme la thérapie comportementale et cognitive (TCC). L'accès à un tel traitement est cependant limité. L'usage de la TCC par Internet (des programmes « self-help » accompagnés d'un bref soutien thérapeutique par courriel) est un moyen prometteur pour augmenter l'accessibilité du traitement.

Le premier objectif de cette thèse était d'examiner si le traitement par Internet était efficace pour réduire des symptômes dépressifs et s'il était possible de prédire quels participants allaient bénéficier d'un tel traitement. Le deuxième objectif de la thèse était, d'une part, d'examiner si le traitement par Internet était efficace pour des patients avec un TP dans un milieu de soins réguliers, en comparaison avec un traitement TCC traditionnel en groupe et, d'autre part, d'examiner le coût-efficacité des deux traitements.

Dans l'Etude I, 85 participants ont été répartis par randomisation entre un traitement par Internet et une condition de contrôle d'attention (un forum de discussion). Des mesures de dépression post traitement ont montré des tailles d'effet larges et cette amélioration était maintenue dans les mesures lors du suivi de 6 mois, montrant donc que le traitement par Internet était efficace pour réduire des symptômes dépressifs. L'Etude II a analysé des prédicteurs du résultat du traitement au suivi de 6 mois de l'Etude I. Le niveau de symptômes dépressifs prétraitement et le nombre d'épisodes de dépression antérieurs étaient associés à une amélioration moins importante.

L'Etude III était un essai ouvert évaluant un traitement par Internet, ayant montré son efficacité avec des participants volontaires dans des études précédentes, dans un milieu de soins psychiatriques réguliers et pour 20 patients avec un TP adressés pour traitement. Lors des mesures post traitement 75% des patients étaient considérés comme ayant une bonne réponse au traitement et la proportion était de 70% lors du suivi de 6 mois, indiquant ainsi qu'il était possible de transférer ce traitement dans un milieu de soins réguliers tout en conservant son efficacité.

L'Etude IV était un essai randomisé contrôlé comparant l'efficacité de la TCC administrée soit par Internet soit en groupe, pour 104 patients dans un milieu de soins psychiatriques. Les deux traitements ont produit des améliorations significatives, et il n'y avait pas de différences statistiquement significatives ni lors des mesures post traitement ni lors du suivi de 6 mois. Une analyse coût-efficacité a montré que le traitement par Internet était plus coût-efficace que le traitement en groupe en ce qui concerne le temps employé par les thérapeutes.

Cette thèse fournit des preuves de l'efficacité du traitement par Internet dans la réduction des symptômes de dépression et de TP, et que ce traitement est aussi efficace que la TCC en groupe pour des patients adressés pour traitement dans un milieu de soins réguliers. Elle fournit aussi des preuves que le traitement par Internet du TP est davantage coût-efficace que le traitement en groupe. En somme, les résultats soutiennent une implémentation du traitement par Internet pour la dépression et le TP dans le milieu de soins réguliers.

Mots clés : dépression, trouble panique, agoraphobie, thérapie comportementale et cognitive, self-help, bibliothérapie, Internet, coût-efficacité.

LIST OF PUBLICATIONS

This thesis is based on the following scientific papers, which henceforth will be referred to in the text by their corresponding Roman numbers.

I. Andersson, G., Bergström, J., Holländare, F., Carlbring, P., Kaldo, V., & Ekselius, L. (2005). Internet-based self-help for depression: a randomised controlled trial. *British Journal of Psychiatry*, *187*, 456-461.

II. Andersson, G., Bergström, J., Holländare, F., Ekselius, L., & Carlbring, P. (2004). Delivering CBT for depression via the Internet. Predicting outcome at 6-months follow-up. *Verhaltenstherapie*, *14*, 185-189.

III. Bergström, J., Andersson, G., Karlsson, A., Andréewitch, S., Rück, C., Carlbring, P., & Lindefors, N. (2009). An open study of the effectiveness of Internet treatment for panic disorder delivered in a psychiatric setting. *Nordic Journal of Psychiatry*, *63*, 44-50.

IV. Bergström, J., Andersson, G., Ljótsson, B., Rück, C., Andréewitch, S., Carlbring, P., Karlsson, A., Andersson, E. & Lindefors, N. (2010) Internet- versus Group-administered Cognitive Behaviour Therapy for Panic Disorder in a Psychiatric Setting: A Randomised Trial. *Submitted manuscript*.

TABLE OF CONTENTS

1 Introduction 3
1.1 Background 4
1.2 Panic disorder and depression 6
1.2.1 Diagnosis of panic disorder 6
1.2.2 Diagnosis of depression 7
1.2.3 Differential diagnosis and comorbidity 8
1.2.4 Prevalence 9
1.2.4.1 Panic disorder 9
1.2.4.2 Depression 9
1.2.5 Phenotype, onset and course 9
1.2.5.1 Panic disorder 9
1.2.5.2 Depression 11
1.2.6 Heredity 12
1.2.6.1 Panic disorder 12
1.2.6.2 Depression 13
1.2.7 Pharmacological treatment 14
1.2.7.1 Panic disorder 15
1.2.7.2 Depression 16
1.3 Psychological treatment of panic disorder and depression 18
1.3.1 Brief background to CBT 18
1.3.2 Panic disorder 19
1.3.3 Depression 20
1.4 Making psychological treatment accessible 23
1.4.1 Self-help and bibliotherapy 23
1.4.1.1 Treatment outcome 24
1.4.2 Internet-based treatment 25
1.4.2.1 Computers, Internet and psychotherapy 25
1.4.2.2 Treatment outcome 27
1.4.2.2.1 Panic Disorder 27
1.4.2.2.2 Depression 29
1.5 From development to deployment 34
1.5.1 Efficacy and effectiveness 34
1.5.2 Cost-effectiveness 35
1.5.3 Development of studies in the thesis 35
2 The empirical studies 37
2.1 Study I. Internet-based self-help for depression: a randomised controlled trial 38
2.1.1 Aims 38
2.1.2 Methods 38
2.1.3 Results 39
2.1.4 Discussion 40
2.2 Study II. Delivering CBT for depression via the Internet. Predicting outcome at 6-months follow-up 41
2.2.1 Aims 41
2.2.2 Methods 41
2.2.3 Results 41

2.2.4 Discussion 42
2.3 Study III. An open study of the effectiveness of Internet treatment for panic disorder delivered in a psychiatric setting 43
2.3.1 Aims 43
2.3.2 Methods 43
2.3.3 Results 44
2.3.4 Discussion 45
2.4 Study IV. Internet- versus Group-administered Cognitive Behaviour Therapy for Panic Disorder in a Psychiatric Setting: A Randomised Trial 46
2.4.1 Aims 46
2.4.2 Methods 46
2.4.3 Results 47
2.4.4 Discussion 48
3 General discussion 49
3.1 Main findings 50
3.2 Therapist- and client factors and the therapeutic relationship 51
3.3 Negative effects and possible risks 53
3.4 Internet treatment and psychotherapy 53
3.5 Clinical implications 55
4 Acknowledgements 57
5 References 61

LIST OF ABBREVIATIONS

AR	Applied relaxation
ASI	Anxiety Sensitivity Inventory
BA	Behavioural activation
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BT	Behaviour therapy
CBT	Cognitive behaviour therapy
CCBT	Computerised cognitive behaviour therapy
CT	Cognitive therapy
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4 ed.)
ES	Effect size
EST	Empirically supported treatment
GAD	General anxiety disorder
GAF	Global Assessment of Function
HADS	Hospital Anxiety and Depression Scale
ICER	Incremental cost-effectiveness ratio
MADRS	Montgomery Åsberg Depression Rating Scale
MD	Major depression
MDD	Major depressive disorder
MDE	Major depressive episode
MI	Mobility Inventory for Agoraphobia
NAT	Negative Automatic Thought
PA	Panic attack
PD	Panic disorder
PDA	Panic disorder with agoraphobia
PDT	Psychodynamic therapy
PDWA	Panic disorder without agoraphobia
PDSS	Panic Disorder Severity Scale
QOLI	Quality of Live Inventory
SDS	Sheehan Disability Scale
SSRI	Selective serotonin reuptake inhibitor

1 INTRODUCTION

1.1 BACKGROUND

Fear, worry and low mood are experiences we all are familiar with and which seem to be inevitable parts of life. For some people however, less fortunate then others, these experiences are not merely episodes of temporary discomfort but rather something that permeates their life altogether.

> *"Everything that could have been a source of compassion, of lust […] has become a source of suffering and despair. Since several years I have walked side by side with a phantom that resembles me, who lives in a theoretical paradise, in close relation to the world. I have for a long time believed that I was to reunite with him. That is now all over. […] The sense of separation is complete, I am hereafter a prisoner in myself."* (Houellebecq, 1994)

When this happens, that is, when normal transient experience turns into debilitating suffering and hinders functioning in daily life, we talk of psychiatric diagnoses.

Major depression (MD) and anxiety disorders are, along with substance abuse and impulse-control disorders, the most common forms of psychiatric illness we know, affecting around 16-17 % and 24-28 % respectively of the adult population in their lifetime (Kessler, Berglund, et al., 2005; Kessler, et al., 1994). The World Health Organization (2002) noted that MD is one of the disorders with the highest disease burden in the world, projected to be the second leading cause of disability worldwide (after heart disease) in 2020 (Murray & Lopez, 1997).

Much effort has been put into trying to diminish the burden of these psychiatric disorders, and two of the most promising developments are the pharmacological treatments known as antidepressants (Arroll, et al., 2009; Cipriani, et al., 2009) and the psychological treatments known as CBTs (cognitive behavioural therapies) (Cuijpers, van Straten, Andersson, & van Oppen, 2008; Norton & Price, 2007).

However, whereas access to pharmacological treatment can be said to be relatively satisfactory, access to evidence-based psychological treatments is still a problem (Richards, Lovell, & McEvoy, 2003). Since patients tend to prefer one or the other treatment and preferences can influence outcome it is important that health care can deliver all evidence-based treatments, in particular for patients who for various reasons can not tolerate one particular treatment (e.g., medication).

In response to this a field of research has emerged which attempts to find ways to make CBT more accessible. This has been done by increasing the patient's own involvement in therapy, notably by different forms of psychological self-help approaches, in which the amount of therapist contact is reduced (den Boer, Wiersma, & Van den Bosch, 2004). Internet-based CBT is such a development that for the last ten years has been found to be an efficacious treatment alternative in research studies (Andersson, 2009; Spek, Cuijpers, et al., 2007), with the potential to increase access to evidence-based

psychological treatments. A number of trials have been conducted evaluating Internet-based CBT for depression and panic disorder (PD). However, it has been unclear how Internet treatment works in regular psychiatric health care settings, with referred patients, and which factors that are important for treatment response.

This doctoral thesis describes the development of Internet-based CBT for depression and PD and the deployment of this treatment form within regular psychiatric health care. By doing so, it wishes to contribute to the important endeavour of making effective psychological treatments more accessible for those in great need of them.

1.2 PANIC DISORDER AND DEPRESSION

1.2.1 Diagnosis of panic disorder

Panic has been a well known condition in the medical literature for a very long time, with the first documentation dating from the late 19th century (Benedikt, 1870). In the dominant diagnostic system of our time, the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2000a), PD is defined by its central feature, the *panic attack* (PA). The DSM-IV defines a PA as a "discrete period of intense fear or discomfort in the absence of real danger" that should arise abruptly and reach its peek within 10 minutes. The DSM-IV lists 13 characteristic symptoms of such an attack and says that at least 4 of them must be present for it to qualify as a full panic attack: 1. Palpitations, pounding heart, or accelerated heart rate, 2. Sweating, 3. Trembling or shaking, 4. Sensations of shortness of breath or smothering, 5. Feeling of choking, 6. Chest pain or chest discomfort, 7. Nausea or abdominal distress, 8. Feeling dizzy, unsteady, lightheaded, or faint, 9. Derealisation or depersonalization, 10. Fear of losing control or going crazy, 11. Fear of dying, 12. Paresthesias (numbness or tingling sensations), 13. Chills or hot flushes.

While being the essential symptom of the disorder, the presence of PAs is not exclusive to PD. Indeed, there is probably no psychiatric disorder where PAs *do not* occasionally occur as a part of a period of elevated anxiety (Goodwin, 2003). For the DSM-IV diagnosis of PD to be made, at least one of the attacks has to be followed by one month (or more) of at least one of these symptoms: 1. Persistent concern about having additional attacks, 2. Worry about the implications of the attack or its consequences, 3. A significant change in behaviour related to the attacks. What emerges after the initial attack(s) is in other words a strong fear of what will happen the next time (e.g. having a stroke, heart attack, or "going crazy") and that the person tries to avoid the situations where the attack(s) took place, in order to prevent this catastrophic outcome.

This latter feature of the disorder, avoidant behaviour, often develops into *agoraphobia*. The DSM-IV defines agoraphobia as "Anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having an unexpected or situationally predisposed PA or panic-like symptoms" and that "The situations are avoided […] or else are endured with marked distress or with anxiety about having a PA or panic-like symptoms, or require the presence of a companion". Typical agoraphobic situations are public transport, closed places (elevators, bathrooms etc.), supermarkets, or, often in more severe cases, simply being alone. A recurrent finding is that among PD patients, comorbid agoraphobia is associated with higher severity, impairment, and other comorbidity (Batelaan, et al., 2010; Kessler, et al., 2006), as well as lower rates of recovery over time (Bruce, et al., 2005)

Since the DSM-III-R (American Psychiatric Association, 1987) this diagnostic system only includes the diagnosis of *PD with agoraphobia* (PDA), *PD without agoraphobia* (PDWA), and *agoraphobia without history of PD*. That is, agoraphobia has not been viewed as a discrete disorder but only diagnosed in relation to PD. This is however inconsistent with research on agoraphobia, which suggests that it is best viewed as a separate diagnosis (Bienvenu, et al., 2006; Wittchen, et al., 2008). The origin of such "pure" agoraphobia can for example be fear of urinary or faecal soiling or vomiting in a public space, with no subjective experience of panic-like symptoms. The research on agoraphobia also suggests that it is potentially just as debilitating as PD. In the upcoming DSM-V, agoraphobia is therefore proposed to become a discrete, independent diagnosis (American Psychiatric Association, 2010a). As a consequence, in the DSM-V, the diagnoses of PDA and PDWA are proposed to disappear, leaving the sole diagnosis of PD (American Psychiatric Association, 2010c), which thus can be comorbid or not with agoraphobia.

The diagnostic confusion surrounding agoraphobia that came with the DSM-III and the primary role that then was given to PAs (Ramnerö & Öst, 2007) is probably the reason for the weakening research interest in agoraphobia since the 1980s (Boschen, 2008). In contrast, research on panic has increased during this period of time.

1.2.2 Diagnosis of depression

Even if known under different names throughout human history, the first to describe depression[1] in the medical literature was the German psychiatrist Emil Kraepelin who in the early 20th century distinguished what he called "involutional melancholia" from the previously described manic-depressive psychosis (Hirshbein, 2006). Since then, much has changed in research and nosology, leading up to what we today call major depressive disorder (MDD). However, the term "melancholia" has been used since much earlier, and at least since the 17th century, for what we today probably would call depression.

If the PA is the central feature in PD, the major depressive episode (MDE) is certainly the main feature of MDD in the DSM-IV (American Psychiatric Association, 2000a). The DSM-IV lists 9 common depressive symptoms and defines a MDE as a "two-week period [that represents] a change from previous functioning" including at least 5 of the 9 symptoms (criterion A). All these symptoms (except the last, 9.) are defined as having to be present "nearly every day". DSM-IV also specifies that at least one of the two primary symptoms (listed first) must be present for the diagnosis to be made. The nine depressive symptoms are: 1. Depressed mood most of the day, 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, 3. Significant weight loss when not dieting or weight gain, 4. Insomnia or hypersomnia, 5. Psychomotor agitation or retardation, 6. Fatigue or loss of energy, 7. Feelings of worthlessness or excessive or inappropriate guilt, 8. Diminished ability to think or

[1] In this thesis the generic term "depression" will be used throughout the text as an generic term including MDD as well as sub-threshold depression and depressive symptoms. These individual terms will be then be made explicit when appropriate.

concentrate, or indecisiveness, 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. As with PA in PD, MDE is the central element in MDD, but does not solely suffice for this diagnosis to be made. In MDD, a MDE can be either single or recurrent (where at least two months have passed between discrete MDEs). One should also specify the severity of the MDE, if it is or not in remission, if it is chronic in nature, if it has catatonic or atypical features, or if it had postpartum onset. There is also the possibility to specify the course of the disorder, by specifying if there is an interepisode recovery or not, and whether there is a seasonal pattern. Following DSM-IV convention it is also said that "the symptoms cause clinically significant distress" (criterion C).

As for the PD and agoraphobia diagnoses, there is however some controversy around the DSM-IV diagnosis of MDD. This line of criticism holds that the DSM-IV requirements for criterion A (two weeks duration and at least five symptoms) and clinically significant impairment (criterion C) have little empirical support for their use (Kendler & Gardner, 1998). It has been argued that depressive symptoms are best understood and described as continuous rather than dichotomous phenomena (Aggen, Neale, & Kendler, 2005). Therefore, there are empirical sound reasons behind the choice of the generic term "depression" in this thesis, as a categorical distinction between MDD, sub-threshold depression and depressive symptoms may not harmonise well with clinical reality. This point will be elaborated upon later when discussing the course of depression (1.2.5.2) and when discussing Study I.

1.2.3 Differential diagnosis and comorbidity

There is a well-documented and strong overlap between PD and MDD (Roy-Byrne, et al., 2000). About 50% of those suffering from PD and 73.3% of those with PDA have a comorbid mood disorder. More specifically, 34.7% and 38.5% respectively have comorbid MDD (Kessler, et al., 2006). In turn, 59.2% of those suffering from MDD have a comorbid anxiety disorder (Kessler, et al., 2003). In the DSM-V, a new diagnosis of Mixed Anxiety Depression is proposed as a free standing diagnosis (American Psychiatric Association, 2010b). Sleep disturbance is known to be highly aggravated by concomitant nocturnal panic attacks and depression (Singareddy & Uhde, 2009)

PD and PDA have high comorbidity rates with other forms of anxiety as well (Kessler, et al., 2006). For example, 66% of PD patients and 93.6% of PDA patients have at least one other comorbid anxiety disorder.

Important differential diagnostics to make among patients with suspected PD is hyperthyroidism and hypothyroidism (Simon, et al., 2002) as well as partial epileptic seizures without generalization, emanating from temporal lobe epilepsy (Deutsch, Rosse, Sud, & Burket, 2009; Hurley, Fisher, & Taber, 2006). Another more rare issue of differential diagnostics reported in the literature is that of temporal brain tumours (Kellner, Hirschmann, & Wiedemann, 1996).

1.2.4 Prevalence

1.2.4.1 Panic disorder

In the large and possibly most rigorous epidemiological study of prevalent psychiatric disorders, the American National Comorbidity Survey Replication (NCS-R), a life-time prevalence of 4.7% was found for PD with or without agoraphobia (Kessler, Berglund, et al., 2005). In a more specific analysis (Kessler, et al., 2006) the life time prevalence for PAs without agoraphobia was 22.7%, for PD without agoraphobia (PDWA) it was 3.7%, and for PD with agoraphobia (PDA) it was 1.1%. Another large epidemiological study (Grant, et al., 2006) showed similar results for lifetime prevalence: 5.1% for PD (with or without agoraphobia), 4.0% for PDWA and 1.1%. for PDA. The rate of lifetime agoraphobia was considerably lower, at 0.17%.

For 12-month prevalence, the NCS-R (Kessler, Chiu, Demler, Merikangas, & Walters, 2005) reported a rate of 2.7% for PD (with or without agoraphobia), and for agoraphobia (without panic) 0.8%. In the study by Grant and colleges (2006) the reported 12-month prevalence was 2.1% for PD, 1.6% for PDWA, 0.6% for PDA, and 0.05% for agoraphobia.

Similar 12-month prevalence of PD is found in Europe, where it is estimated at 1.8% (Goodwin, et al., 2005). In a Swedish study (Carlbring, Gustafsson, Ekselius, & Andersson, 2002), the 12-month prevalence of PD was 2.2%.

1.2.4.2 Depression

There are considerable differences between reported prevalence rates of MDD around the world, ranging between 4% and 20% on rates of lifetime prevalence (Andrade, et al., 2003). It is very difficult to judge whether these differences reflect actual variation in rates of depressive illness or if they simply reflect the difficulties of defining depression recently evoked; that is if they result from different criteria used to establish diagnosis and from related methodological features of the studies that influence accuracy of the results obtained.

In the NCS-R (Kessler, et al., 2003; Kessler, Berglund, et al., 2005) a life time prevalence of 16.6% was found for MDD, while the 12-month prevalence found (Kessler, Chiu, et al., 2005) was 6.7%. There are considerable sex differences in the prevalence MDD, with women having a life time prevalence of around 20% and men 12% (Kessler, et al., 2003).

1.2.5 Phenotype, onset and course

1.2.5.1 Panic disorder

The mean age of onset for PDWA and PDA has been estimated to be 23.6 years and 22.9 years respectively (Kessler, et al., 2006). However, some data support that the age

onset has a bimodal distribution (Eaton, Kessler, Wittchen, & Magee, 1994), with two clusters, the first being in the range of 15-24 years and the latter, more representative of women, being in the 45-54 year range. In certain studies however a different pattern is found, with a mean age of onset of approximately 34 years, with no substantial gender differences concerning age of onset (Yonkers, Bruce, Dyck, & Keller, 2003).

PD is known to occur among women more often than among men, this disorder probably being more than twice as prevalent among women (Carlbring, et al., 2002; Eaton, et al., 1998). The expression of PD differs as well; men having, besides an earlier age of onset, a shorter duration of illness. Men are also less afflicted by agoraphobia but present significantly more often a history of alcohol and/or substance dependence/abuse (Clayton, Stewart, Fayyad, & Clary, 2006).

As discussed earlier, agoraphobia has traditionally been seen as merely an effect of un-treated PD. In other words, that PD would predict future onset of agoraphobia and not vice-versa. However longitudinal findings show that primary agoraphobia also predicts future onset of PD (Bienvenu, et al., 2006), agoraphobia being in fact the only DSM disorder to do so robustly. Agoraphobia may as well be equally related to depression as to PAs. In behavioural treatment research a change in avoidance has been seen to be more related to change in negative affect than to change in PAs (Ramnerö & Öst, 2007).

The course of PD shows that spontaneous remission from PD is more common than in other anxiety disorders. This is however only true if there is no comorbid agoraphobia. PDA is thus, in contrast with PDWA, alongside social phobia, the most chronic anxiety disorder with a majority of patients still suffering from the disorder at least 8 years after onset (Yonkers, et al., 2003).

Nocturnal PAs occur in 18% to 45% of PD patients (Craske, et al., 2002). There are conflicting views on its association with overall PD severity but according to a recent study (Albert, Maina, Bergesio, & Bogetto, 2006) nocturnal PAs does not seem to indicate higher severity or elevated comorbidity.

Some research show that personality disorder traits, especially avoidant and dependant personality, present from early adulthood, may contribute to an increased risk for the development of PD and agoraphobia later in life (Bienvenu, et al., 2009; Johnson, Cohen, Kasen, & Brook, 2006). They may also increase clinical severity of comorbid PD (Ozkan & Altindag, 2005). Other risk factors may include childhood sexual abuse (Katerndahl, Burge, & Kellogg, 2005).

PA and PD have also been shown to be associated with coronary heart disease and acute myocardial infarction, at least in younger patients (Walters, Rait, Petersen, Williams, & Nazareth, 2008). Whether this reflects that PA/PD causes physiological changes that elevates the risk of heart disease, or if it simply reflects initial misdiagnosis of coronary heart disease and acute myocardial infarction by general practitioners, is however not clear.

1.2.5.2 Depression

The median age of onset for a MDE is in the range of 20 to 25 years (Andrade, et al., 2003) whereas its mean duration has been found to be 16 weeks (Kessler, et al., 2003). Research shows that MDEs have a high recurrence rate, and that chronicity often develops over time. Solomon and co-workers (2000) found that after the initial episode, 2/3 of those afflicted experienced at least one recurrence of MDE, and the risk of future relapse then progressed so that the risk of recurrence increased by 16% with each new MDE. Moreover, the median time to relapse decreased over time with multiple episodes; the median time for the first prospectively observed recurrence was 150 weeks, for the second recurrence it was 83 weeks, and then it continued to shorten with new episodes. However, as the duration of recovery increased, the risk of recurrence decreased.

Depression can thus be called a "waxing and waning" phenomenon which is dominated by relapse, and often, by prolonged chronicity where symptom severity changes over time in the same patient and where 1/4 of patients after a MDE still will have chronic residual symptoms with merely incomplete remission over several years (Judd, et al., 1998). In other words, depression is a condition both intermittent and chronic. Persons afflicted by it typically have recurrent episodes that persist, but for less than 12-months (Andrade, et al., 2003).

Chronic depression has been associated with lower age of onset, elevated suicidality, comorbid PD and substance abuse as well as higher rates of familial aggregation (Mondimore, et al., 2006). There is both cross-sectional and longitudinal evidence that stressful life experiences predict onset of MDEs (Pine, Cohen, Johnson, & Brook, 2002). It is hypothesized that this is due to stress affecting brain plasticity (Duman, Malberg, & Thome, 1999). Among those with MDD, 49% suffer from a mild or moderate form of the disorder whereas 39% have severe symptoms and 13% very severe (Kessler, et al., 2003).

In the depressive phenotype, certain characteristics may be particularly important for understanding the differential severity among those afflicted. One such characteristic is the depressive trait of irritability, present in DSM-IV MDD-diagnosis among children and adolescents but not in the adult diagnosis. Irritability has been shown to be specifically associated to early age of onset, chronicity, comorbidity with anxiety and impulse-control disorders, fatigue and self-reproach during episodes, as well as higher disability (Fava, et al., 2009).

As it is often a chronic condition, one would expect depression to be highly prevalent in old age. However, even if old age poses an elevated risk for depression resulting from vascular changes or other age-related physical disorders, it is known that MD actually decline towards old age (Jorm, 2000), which could be explained by the increase of other psychological protective factors that develop with age (Blazer, 2005). On the other hand, there is evidence that depressive symptoms could be a risk factor for decline in physical performance and disability in activities of daily living (ADL), even at subclinical levels (Hybels, Pieper, & Blazer, 2009).

1.2.6 Heredity

1.2.6.1 Panic disorder

There is strong support in the research literature for familial aggregation of PD, with risk estimates for PD in first-degree relatives of PD probands ranging from 7.9 to 17.3% compared to 0.7-4.2% in first-degree relatives of controls (Shih, Belmonte, & Zandi, 2004). This risk of familial heredity seems particularly prominent among female first-degree relatives (Maier, Lichtermann, Minges, Oehrlein, & Franke, 1993). Heredity in general seems however specific to PD, whereas the familial liability of agoraphobia is less clear (Nocon, et al., 2008).

There is also specific support for a genetic contribution to the development of PD, and a meta-analysis of twin studies describes a genetic contribution of 43% (Hettema, Neale, & Kendler, 2001). Studies overall show a 2-3 times higher concordance rate among dizygotic then among monozygotic twins (Shih, et al., 2004).

What genes do then account for these genetic differences? Because of the known effect of serotonergic drugs for PD, the influence of the serotonin system and more specifically the serotonin transporter protein (5-HTT) has become a major focus of research on candidate genes (Bell & Nutt, 1998; Lesch, et al., 1996). One such gene is the 5-HTT-linked polymorphic region (5-HTTLPR) located on chromosome 17. It is a functional 43BP insertion/deletion polymorphism[2] yielding a short (*s*) or long allele (*l*)[3]. The s-allele has been shown to be associated with amygdale reactivity (neural correlate of fear response) (Munafo, Brown, & Hariri, 2008) and neuroticism (Munafo, et al., 2009). Moreover, it has recently been shown that it is more specifically involved in fear learning by amplifying the startle response (Lonsdorf, Weike, et al., 2009). However, its association to the diagnostic entity of PD is not conclusive (Blaya, Salum, Lima, Leistner-Segal, & Manfro, 2007).

In a study by our group (Lonsdorf, Rück, et al., 2009) patients from Study IV were asked to participate in an additional study, by giving permission to genetic analysis of blood samples. The methods used in the study are detailed elsewhere (Lonsdorf, Rück, et al., 2009). We investigated the association of 5-HTTLPR and symptom severity among PD patients using the Panic Disorder Severity Scale (PDSS) scores (see Study IV). Besides the biallelic analysis (of *s* and *l* alleles), a triallelic analysis was also performed including a SNP (A→G) located in conjunction with the 5-HTTLPR. The G-allele of this SNP has been shown (as has the *s* allele in 5-HTTLPR) to reduce serotonin (5-HT) expression in the brain (Kraft, Slager, McGrath, & Hamilton, 2005). One previous (case-control) study has analysed the association between triallelic 5-HTTLPR and PD, showing no relation (Strug, et al., 2010).

---

[2] A *base pair* (BP) consists of two nucleotides (the molecules structuring DNA) connected by a hydrogen bond, on opposite sides of the DNA strand. Several BPs form a DNA sequence. *Polymorphism* denotes a variation in a single BP (single nucleotide polymorphism, SNP), or in a sequence of BPs, that is common in the population.

[3] An *allele* denotes one variant of a polymorphism at particular place along the DNA strand. In this case, "43BP insertion/deletion" means that the short allele lacks 43BP that the long allele has.

The results of our study showed that patients with the 5-HTTLPR *s*-allele did have a significant higher panic severity (as measured by the PDSS), thus showing an association between 5-HTTLPR and panic, in contrast with much earlier research. This stresses the importance of a more fine-tuned definition of the phenotype of interest. Much psychiatric genetic research has probably too heavily relied on case-control studies and the quite crude entities of DSM-IV diagnoses. Continuous ratings such as the PDSS is simply better than dichotomous diagnostics in reflecting the phenotypic variance of PD, an issue which has been previously discussed in the literature (Smoller & Tsuang, 1998). In our study we analyzed not diagnosis but symptomatic profile and could thus find an association that would have been lost in the traditional case-control design. Our data thus highlight the importance of defining appropriate phenotypes for psychiatric genetic studies.

In a second study by our group (Lonsdorf, et al., 2010), again using blood samples from patients in Study IV, we examined the role of the functional polymorhpism COMTval158met[4] for understanding response pattern in our CBT treatment. The met-allele has previously been shown to be associated with, among other things, resistance to fear extinction in experimental settings (Lonsdorf, Weike, et al., 2009) and was therefore examined in this trial, whose methods are detailed elsewhere (Lonsdorf, et al., 2010). The most significant result of this study was that patients with the met/met genotype showed significantly less symptom relief during the exposure modules of the treatment (modules 6 to 9, see Study IV for details) as compared to COMT 158val-carriers. We thus found tentative evidence that PD patients with the met/met genotype (compared to those with at least one val-allele) may not respond as well to exposure in-vivo as part of a CBT treatment. This is significant, in the sense that it reflects earlier experimental findings of the effect of the COMTval158met polymorphism on extinction of fear, which is posited to be the mechanism of action behind the therapeutic effects of exposure.

Future research in the direction that these two studies have marked out may hopefully allow a finer understanding of the genetic contributions to the development and clinical manifestation of PD as well as to a better understanding of treatment response patterns in pharmacological as well as in psychological treatment.

1.2.6.2 Depression

MDD is considered to be a heterogeneous and moderately heritable disorder, with the greatest familial risk among those with recurrence of MDEs, worse impairment, and early age of onset (Levinson, 2006; Milne, et al., 2009), although the latter is less conclusive. Relatives of probands with bipolar disorder (BD) show higher risk of developing MDD, whereas the reverse is not the case (McGuffin, et al., 2003).

[4] val158met is a functional single nucleotide polymorphism (SNP) of the gene for catechol-O-methyl transferase (COMT) that has been shown to be related to many functions, among them cognitive tasks and fear extinction.

Studies on the genetic contribution to MDD comparing concordance rates between monozygotic and dizygotic twins reveal a heritability of about 37% (Sullivan, Neale, & Kendler, 2000). This heritability is higher in women (42%) than in men (29%) (Kendler, Gatz, Gardner, & Pedersen, 2006). It has also been shown in a twin study that at least among women, genes modify the susceptibility to stressful life experiences and therefore influences onset of MDD (Kendler, et al., 1995).

The question is then which candidate genes that could account for these findings. In this line of research the 5-HTTLPR (Lesch, et al., 1996) mentioned earlier has also been associated with neural correlates connected to depressive symptoms (Pezawas, et al., 2005). Evidence for its direct relation to MDD is however inconclusive (Lesch, 2003), but research has revealed that if not directly related to depression, it could well be indirectly related by moderating the serotonergic response to stressful life events (Levinson, 2006).

In a much-cited prospective epidemiologic study, Caspi and co-workers (2003) found that the 5-HTTLPR predicted onset of depression, but only in association with stressful life experiences. More specifically, carriers of the *s* allele showed more depressive symptoms, MDD diagnosis, and suicidality in relation to stressful life experiences than carriers of two *l* alleles (homozygous). It was suggested that this observed interaction between genes and environment could be explained epigenetically, that is, that environmental factors produce a predisposition to depression by altering gene expression. However, even if this study has been partly replicated, a recent meta-analysis (Risch, et al., 2009) has called into question this "serotonin gene-life stress hypothesis". The meta-analysis concludes that 5-HTTLPR does not improve the prediction of risk of MDD beyond that associated with exposure to stressful life experiences, the latter being a known risk factor for MDD-onset (Pine, et al., 2002).

Genetic research on broadly defined diagnostic entities such as PD, and to an even higher degree MDD, has increasingly been called into question, because of the large genetic heterogeneity associated with these disorders. As discussed above concerning PD and the studies by our group (Lonsdorf, Rück, et al., 2009; Lonsdorf, et al., 2010), future research lies probably in defining less broad phenotypes such as symptomatic profiles (not necessarily related to diagnosis), as these may identify cases that share genotype.

1.2.7 Pharmacological treatment

There are a number of groups of pharmacological agents, most of them used for both PD and MDD, who have shown to be effective in treating these disorders. They are the selective serotonin reuptake inhibitors (SSRI) and serotonin/noradrenaline reuptake inhibitors (SNRI), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and the anxiolytics (benzodiazepines).

SSRI/SNRIs, often called the "new generation antidepressants" have been introduced for the treatment of PD and MDD the past 20 years. They affect the reuptake of serotonin and/or noradrenalin in the synaptic cleft by altering the function of the

proteins SERT (serotonin transporter) and NAT (noradrenalin transporter) (Artigas, Nutt, & Shelton, 2002). Examples of such drugs are citalopram, escitalopram, duloxetine, fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine.

TCAs are a group of early antidepressant drugs, introduced in the 1950s. Most TCAs function by altering the function of SERT and NAT, as do the SNRIs (Stahl, 1998). Examples of these drugs are amitriptyline, nortriptyline, clomipramine and imipramine.

MAOIs are another older group of drugs that have in common that they inhibit the activity of the enzyme MAO, and thus effect transmission of monoamine neurotransmitters such as serotonin, noradrenaline and dopamine. Different MAOIs are more selective than others as to which neurotransmitters they affect (Stahl, 1998). There are two different forms, the early irreversible MAOIs and the more recent reversible MAOIs. Examples are phenelzine, moclobemide and selegiline.

Among anxiolytics the most common group of drugs are the benzodiazepines (BZDs). The shared mechanism of action of these structurally related drugs is their effect on the neurotransmitter gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system (CNS) (Campo-Soria, Chang, & Weiss, 2006). These drugs are categorized following their short-, intermediate- or long-acting effect, which depend upon their half-life properties. Examples are alprazolam, clonazepam, diazepam, flunitrazepam, and oxazepam.

1.2.7.1 Panic disorder

SSRI/SNRIs constitutes the pharmacological treatment of choice for PD (American Psychiatric Association, 1998), and are considered rather homogenous in their efficacy profile, whereas differences rather can be found when it comes to issues of safety and side effects. Common side effects are gastrointestinal symptoms, agitation, sleep disturbance, weight gain and impaired sexual function and/or desire, however considered less prominent than among earlier pharmacological treatments (Dannon, et al., 2007). Paroxetine distinguishes itself from the other SSRIs because of its additional effect on the noradrenergic and cholinergic system, hypothesized to account for a mild sedating effect and thus to be of possibly additional value in the treatment of PD. If there is no robust support for strong differential gender effects from SSRIs, there is some evidence that women possibly could benefit more from certain SSRIs at least when it comes to reduce panic frequency (Clayton, et al., 2006).

Since the 1960 the effects of TCAs on PD has been known (Klein, 1964) through several reports in support for their efficacy (Barlow, Gorman, Shear, & Woods, 2000; Mavissakalian & Perel, 1995) but there are concerns surrounding their use. Among those concerns one finds numerous side effects including tremors, weight gain, and sexual dysfunction (Roy-Byrne & Cowley, 2002) as well as possible hypertension (Louie, Louie, & Lannon, 1992). Since the introduction of the SSRIs the role of TCAs has thus become less clinically important. Even if showing similar efficacy, SSRIs are better tolerated than TCAs (Bakker, van Balkom, & Spinhoven, 2002)

The MAOIs have been shown to be effective in PD treatment as well (Riederer, Lachenmayer, & Laux, 2004; Sheehan, 1984). However, being a group of drugs that effect broad neuronal systems in the body, especially the first generation of MAOI drugs are known to have substantial side effects. Particularly first-generation MAOIs are also accompanied by dietary restrictions (Sweet, et al., 1995).

BZDs are still the most commonly prescribed pharmacological treatment for PD (Bruce, et al., 2003), and have been shown to be effective in reducing PD symptoms (Ballenger, et al., 1988; Schweizer, et al., 1990). However, discontinuation and soon relapse are also known problems (Chouinard, 2004). A large issue surrounding BZDs is the one of dependence (Ashton, 2005). While it is clear that many patients demonstrate addiction to BZDs, many researchers judge that it is inconclusive whether this reflects an underpinning (physical) dependence or is best construed as a psychological addiction (de las Cuevas, Sanz, & de la Fuente, 2003).

1.2.7.2 Depression

Somewhat over half of those (57.3%) suffering from MDD receive some form of treatment (Kessler, et al., 2003), primarily SSRIs. As in PD, SSRIs are considered the pharmacological treatment of choice for MDD (American Psychiatric Association, 2000b).

SSRI/SNRI medication is often considered to have similar efficacy and acceptability profiles when it comes to treating MDD (see treatment for PD, above). However, in a recent large meta-analysis (Cipriani, et al., 2009) including 117 studies and 25 928 individuals randomly assigned to 12 different antidepressants, sertraline was considered the best medication when drawing together considerations on efficacy, acceptability, and acquisition cost.

SSRIs and TCAs are considered to be equally effective in treating MDD, but SSRI/SNRIs seem to be better tolerated with less side effects (MacGillivray, et al., 2003). A higher risk for development of coronary heard disease (CHD) is a serious possible side effect of TCAs that has been evoked (Rosenberg, et al., 2010). A major issue in SSRI and TCA treatment is that of relapse prevention, where data suggest that continued treatment can reduce risk of relapse by 70% (Geddes, et al., 2003). However, data suggest that in reality, maintenance of pharmacotherapy for MDD may be relatively poor (Holma, Holma, Melartin, & Isometsa, 2008).

The MAOIs have most often been used in the treatment of so called atypical depression, and have been shown to be selectively more efficacious than other antidepressants for this subgroup of depressive symptoms (Thase, 2007). These symptoms distinguish themselves from classical depressive symptoms such as psychomotor inhibition, loss of sleep (insomnia) and appetite, energy and interest. Atypical symptoms are instead characterised by heightened emotional reactivity and interpersonal sensitivity, increased sleep (hypersomnia), increased appetite and weight gain, and fatigue (Thase, 2007).

Anxiolytics (benzodiazepines) are primarily used as adjuncts to antidepressant treatment for MDD, and there is support for their efficacy in the treatment of patients with prominent comorbid anxiety symptoms, a treatment rational commonly used in clinical settings (Dunlop & Davis, 2008).

1.3 PSYCHOLOGICAL TREATMENT OF PANIC DISORDER AND DEPRESSION

1.3.1 Brief background to CBT

Behaviour therapy (BT) has its theoretical roots in the experimental psychology of learning and in what is known as the radical behaviourism of B.F. Skinner (1988). It is built upon the principles of respondent ("classical") and operant conditioning (Skinner, 1965). This tradition applies the methods of natural science to the study of human behaviour, but originally by way of experimentally studying animal behaviour (Skinner, 1975). The principle of respondent conditioning, first described by the physiologist Ivan Pavlov (1927), means that previously neutral stimuli can acquire the functions of stimuli with which they were paired closely in time (Lavond & Steinmetz, 2003). The principle of operant conditioning means that behaviour is (also) governed by its consequences, by way of being either reinforced (increase in future behaviour) or punished (decrease in future behaviour). Behaviour can both be positively reinforced (the consequence being the presentation of an appetitive stimulus) or negatively reinforced (the consequence being the removal of a pre-existing aversive stimulus, or the non-appearance of an expected aversive stimulus). The concept of punishment, for clinical implications less important than that of reinforcement, can also be divided into positive punishment (the consequence of the behaviour being the presentation of an aversive stimulus) and negative punishment (or "response cost", the consequence of the behaviour being the removal of an appetitive stimulus). Taking these principles together and applying them to the behaviour of a specific individual is called functional analysis (Ramnerö & Törneke, 2008), which is the basic analytical tool used in what is called applied behaviour analysis (ABA) (Austin & Carr, 2000) and in what was to become BT (Eysenck, 1960). Two basic assumptions in BT are: (1) the clinical approach can use the experimental methodology otherwise used in research (measuring, hypothesizing, testing, etc), and (2) dysfunctional behaviours (as in phobias, panic and depression) are acquired in the same manner as other, "normal" behaviours. As a consequence, new learning experiences (acquired for instance during therapy) can come to change the old ones.

Former psychoanalyst Aaron T. Beck is considered to be the "father" of cognitive therapy (CT), which he developed originally in the psychotherapy of patients with depression (Beck, Rush, Shaw, & Emery, 1979), but is now a form of psychotherapy for many different psychiatric disorders. The theory underpinning CT holds that cognitions are the fundamental causal agents behind emotion and behaviour, often named negative automatic thoughts (NATs) (Beck, 1995). NATs arise when something in the environment activates dysfunctional "schemas" (mental structures posited to have evolved during earlier life experiences). A fundamental CT technique is to make NATs apparent, by way of for instance thought records, and then to dispute these thoughts, by way of cognitive restructuring techniques (Beck, 1995).

Cognitive behaviour therapy (CBT) can be said to be an amalgam of CT and BT, where therapeutic techniques stemming from both cognitive and behaviour therapy are used. Behavioural techniques such as behavioural activation (BA) and exposure in-vivo were from the very start integrative parts of CT, although given other names and integrated into a cognitive rational for their therapeutic use (see below).

A more specific description of psychotherapy models and techniques as well as their empirical support will now be given below.

1.3.2 Panic disorder

The earliest reports of the efficacy of behavioural treatments for agoraphobia and panic, based on respondent- and operant principles, emerged in the 1960s, however focusing more on agoraphobic avoidance than on panic symptoms per se (Agras, Leitenberg, & Barlow, 1968; Gelder & Marks, 1966). These as well as subsequent behavioural treatments focus on the patient's avoidance of both internal and external anxiety cues. In other words, panic- and agoraphobic symptoms are construed as resulting from both respondent and operant behavioural processes. First, by way of classical conditioning, a previously neutral stimulus (like a crowded public space or the bodily sensation of slightly elevated heartbeat) becomes a conditioned stimulus eliciting a fear response. If the individual would reengage the same situation several times, without escaping, the fear response would be extinguished. However, what maintains the fear response in the long run are the negatively reinforced escape and avoidance behaviours engaged in by the individual preventing extinction of the fear (Barlow, 2002). From this behavioural account follows that treatment should incorporate exposure to the feared stimuli and prevent escape and avoidance, after which the fear response will extinguish. In PD, this can involve both in-vivo- and interoceptive exposure, that is, exposure to both external stimuli (like crowded public spaces) and internal stimuli (like elevated heartbeat).

Up until the 1980s David H. Barlow and co-workers continued their research initiated in the 1960s, increasingly focusing also on PAs (Barlow, et al., 1984), resulting in a CBT-treatment package called Panic Control Treatment (PCT). At this point it had also come to include cognitive interventions (Barlow & Craske, 2000).

The interest in cognitive therapy and theory increased markedly in the 1980s. In a seminal article, David M. Clark proposed a cognitive conceptualisation of PA and PD (Clark, 1986), pursuing the work on anxiety by Aaron T. Beck (Beck, Emery, & Greenberg, 1985). This model proposed that a PA arises from patient misinterpretations (cognitions) of bodily sensations (as for instance slightly elevated heart rate) as a sign of danger ("Maybe I'm having a heart attack!") which in turn will elevate the sympathetic nervous response even further, entailing a vicious circle of anxiety symptoms and catastrophic cognitions, eventually culminating in a panic attack. To break this vicious circle, cognitive therapy involves the making apparent of these NATs, and then to engage in cognitive restructuring, that is, to modify the fear-inducing content of the thoughts and developing a more realistic cognitive appraisal of the physiological symptoms. The cognitive account also includes a focus on avoidance behaviours, but they are interpreted differently in the cognitive model than within the

behavioural approach (where they are seen as negatively reinforced avoidance behaviours preventing extinction of the fear response). In cognitive therapy the goal is still behaviour change (i.e. encouraging the patient to cease doing avoidance behaviours), but the proposed mechanism of action is construed as that by doing so fear-related cognitions are altered, and the previous causes of PAs are therefore dismantled (Beck, et al., 1985; Beck, et al., 1979).

An other treatment within the behavioural tradition is applied relaxation (AR) (Öst, 1987), which teaches the patient to recognize early cues of anxiety, and to then to cope with the anxiety in these situations by engaging in a relaxation technique, first learned in non-threatening situations. There is evidence that AR is equally effective as exposure treatment as well as CBT in the treatment of PDA (Öst, Westling, & Hellström, 1993) and that it is equally effective as CBT in the treatment for PDWA (Öst & Westling, 1995), with symptom reductions sustained at 12-month follow-up.

There is extensive evidence for the efficacy of CBT for PD (with or without agoraphobia) in reducing panic and related symptoms, both in acute phase and in follow-up (Clum & Surls, 1993; Mitte, 2005; van Balkom, et al., 1997; Westen & Morrison, 2001) as well as evidence for the specificity of CBT effect on PD (Siev & Chambless, 2007). CBT is thus the most clearly *empirically supported treatment* (EST) (Chambless & Hollon, 1998) for PD. CBT and BT seems to render similar results in treatment of PDA (Öst, Thulin, & Ramnerö, 2004), whereas there is some evidence that CBT reduces attrition and is more effective in reducing comorbid depressive symptoms. The best evidence for the treatment of agoraphobic symptoms seems to be in-vivo exposure, but agoraphobic severity is a negative predictor of treatment outcome (Ramnerö & Öst, 2004). There is evidence that combining pharmacological treatments and CBT/BT is more effective than either treatment alone in the acute treatment phase of PD (with or without agoraphobia) but that there may be an advantage for CBT/BT when long-term effect, discontinuation and side-effects are taken into account (Furukawa, Watanabe, & Churchill, 2006)

A specific model for the psychodynamic understanding of PD has been developed, called panic-focused psychodynamic psychotherapy (PFPP). It states that unconscious fantasies can underlie panic symptoms, and that a PA can be understood as the result of intrapsychic conflict. This psychodynamic treatment has been evaluated in one RCT (Milrod, et al., 2007). In this trial 49 patients were randomised to either PFPP or a treatment that was called applied relaxation (AR). The results showed that PFPP patients had a significantly greater reduction in panic symptoms than those in the comparison condition, as well as a higher response rate. However, it is less than clear if the AR treatment actually was in accordance with the behavioural coping technique developed by Öst (1987).

1.3.3 Depression

As with anxiety the first accounts of a theoretical understanding of depression within the CBT tradition stems from operant principles. Charles B. Ferster, one of Skinners students and collaborators, published in 1973 a seminal work on the functional analysis

of depression (Ferster, 1973) where he stipulated that depression can be explained by a reduction in positively reinforced behaviours and in an increase in negatively reinforced escape- and avoidance behaviours, including also verbal behaviours like complaining. From this account follows that effective treatment should focus on monitoring daily activities and mood, and aim to increase positively reinforced behaviour (often called "pleasurable activities") (Lewinsohn, Munoz, Youngren, & Zeiss, 1986).

While behavioural interest in the treatment of depression grew during the 1970, much following the work of Peter M. Lewinsohn (1974), relatively soon research and clinical work became dominated by Becks CT (Beck, et al., 1979). CT stipulates that low mood and other depressive symptoms are caused by NATs and that the therapeutic goal is, as in CT for PD, to dispute these thoughts using different cognitive restructuring techniques. Just as in CT for PD however, the CT model for depression has always included behavioural techniques, but administered with a cognitive treatment rational.

In 1996 Neil Jacobson and co-workers (1996) published a component analysis of CT for depression showing that the specific cognitive therapeutic techniques were not necessary to obtain treatment effect; that is, that the behavioural techniques on their own were just as effective as the whole CT treatment package. Subsequent trials have confirmed these results, also in long-term follow-up and in comparison to pharmacotherapy (Cuijpers, van Straten, & Warmerdam, 2007; Dimidjian, et al., 2006; Dobson, et al., 2008; Gortner, Gollan, Dobson, & Jacobson, 1998). This called into question the cognitive model of depression and gave birth to a renewed interest in behaviour therapy for depression, in the form of a specific behavioural treatment model called behavioural activation (BA) (Hopko, Lejuez, Ruggiero, & Eifert, 2003; Martell, Addis, & Jacobson, 2001)

Several meta-analyses demonstrate that CT/CBT is an effective treatment intervention for depression both after the acute treatment phase and at follow-up, with moderate to large effect sizes (ES), but with possibly only partial success in preventing relapse (Dobson, 1989; Gloaguen, Cottraux, Cucherat, & Blackburn, 1998; Reinecke, Ryan, & DuBois, 1998; Vittengl, Clark, Dunn, & Jarrett, 2007). BA alone has also shown to be an effective treatment, demonstrating a large ES (Cuijpers, et al., 2007) that is comparable to studies of CBT (Mazzucchelli, Kane, & Rees, 2009).

Another treatment evaluated in treatment of depression is brief psychodynamic therapy or short-term psychodynamic psychotherapy (STPP). The theoretical base of this treatment is psychoanalytic theory and focuses on certain intrapsychic conflicts, but being more time-limited and "here and now"-oriented and with a more active therapist than in traditional psychodynamic therapy (PDT) (Messer & Warren, 1995). There is evidence that STPP is effective in reducing mild to moderate depressive symptoms, and that it is equally effective as CBT in this regard (Cuijpers, et al., 2008; Leichsenring, 2001).

Interpersonal therapy (IPT) is often, but not always, considered to be a form of brief PDT (Leichsenring, Rabung, & Leibing, 2004; Markowitz, Svartberg, & Swartz, 1998). However, whereas STPP is largely a generic therapy, less structured and focused on

intrapsychic conflict, IPT is a depression specific, structured and more pragmatic therapy focusing on the patients interpersonal problems (Markowitz, et al., 1998).

In comparison to antidepressant medication, the large, field-based and much-cited NIMH Treatment of Depression study (Elkin, et al., 1989) showed that CT was as effective as interpersonal therapy but that both psychological treatments were less effective than the TCA imipramine. There is however later evidence that CT/BA is as effective as anti-depressant medication, even in severely depressed out-patients (DeRubeis, Gelfand, Tang, & Simons, 1999; DeRubeis, et al., 2005; Dimidjian, et al., 2006) and also in preventing relapse after discontinuation (Dobson, et al., 2008; Hollon, et al., 2005). There is some evidence that the combination of anti-depressant medication and psychological treatments renders superior treatment effects than psychological treatment alone in acute treatment phase (Cuijpers, van Straten, Warmerdam, & Andersson, 2009), however this may not be the case at follow-up, or when CBT specifically is combined with pharmacotherapy.

Comparing IPT, PDT and CBT in a meta-analysis, Cuijpers and co-workers (2008) found no significant differences in treatment effect, besides that IPT could possibly be more efficacious than the other treatments for mild to moderate depression. In a recent subsequent meta-analysis Cuijpers et al. (2009) holds however that effects of psychological treatments for depression in fact have been generally over-estimated, by not taking into account the quality of studies analysed.

1.4 MAKING PSYCHOLOGICAL TREATMENT ACCESSIBLE

As discussed above, both depression and PD are common psychiatric conditions which cause a heavy disease burden, and for which we know of effective treatments, both psychological and pharmacological. However, whereas access to pharmacological treatments may be said to be satisfactory, access to the empirically supported psychological treatments is still a great concern that public policy makers increasingly have started to call attention to (Clark, et al., 2009). That is, the research literature clearly shows that there are numerous efficacious psychological treatments for depression and PD, but these treatments do not, to a sufficient degree, reach patients in the health care system, largely due to the lack of therapists trained in these treatments. How can this state of affairs be changed? One solution has been to increase the patient's own involvement in therapy and decreasing the presence of the therapist, notably by different forms of psychological self-help approaches and by briefer therapist contact (den Boer, et al., 2004; Richards, Lovell, et al., 2003).

1.4.1 Self-help and bibliotherapy

The term "bibliotherapy", although earlier broadly defined as all written materials, including literary fiction, used to alleviate physical or psychological problems (Alston, 1962), has increasingly been used to denote the use of specific self-help books in the treatment of psychiatric problems. By the mid 1970s researchers within the behavioural tradition had started to evaluate the effects of behavioural bibliotherapy (Goldiamond, 1976; Rosen, Glasgow, & Barrera, 1976). That this evolved within behaviour therapy is understandable given its focus on learning principles and the proposed mechanism of action which is concrete behaviour change. As manuals have always been used within this tradition, it has since the beginning, for the sense of clarity, been important to make the distinction between, on the one hand, "pure self-help", called self-administered treatments, and on the other hand, therapist-administered treatments (Glasgow & Rosen, 1978). Between these two one finds the term "minimal-contact therapy" or "guided self-help", namely when the treatment fundamentally relies on the patient's own appropriation of the treatment manual, but where a therapist gives support, by for instance brief telephone or e-mail contact. Therapist-administered treatment (using a treatment manual) is in turn contrasted with therapist *directed* treatment, where a manual is not used and the whole treatment relies on contact with the therapist (Glasgow & Rosen, 1978). Internet-based treatment, discussed in detail below, should be seen as an example of guided self-help in this regard.

There is a relatively large evidence base for the efficacy of self-help approaches, with various degrees of therapist involvement, both for depressive symptoms (Anderson, et al., 2005; Cuijpers, 1997; McKendree-Smith, Floyd, & Scogin, 2003) and PD

(Carlbring, Westling, & Andersson, 2000; Gould, Clum, & Shapiro, 1993). This evidence will be reviewed below.

1.4.1.1 Treatment outcome

A meta-analysis on bibliotherapy for depression by Pim Cuijpers (1997) included 6 studies that evaluated CBT programmes with either predominantly cognitive (Burns, 1999) or behavioural (Lewinsohn, et al., 1986) content. All studies in this meta-analysis included therapist contact, which in most cases was on a weekly basis. It reflects thus what has been called guided self-help. The comparisons of bibliotherapy and waiting-list yielded a large average between-group effect size of Cohen's d=0.82. Analysing the comparisons of guided bibliotherapy and individual therapy, the effect size was d=0.10, indicating no important differences in efficacy. In a subsequent meta-analysis of 20 studies evaluating a specific bibliotherapy, namely Peter Lewinsohns "Coping with depression course" (CWD) (1984), Cuijpers (1998) showed that compared to control conditions, CWD (including therapist/"teacher" contact) rendered a mean between-group effect size of d=0.65, while the within-group effect size was d=1.21.

In a later meta-analysis on CBT-based bibliotherapy for depression, less methodologically stringent, Gregory and co-workers (2004) included more studies than the previous analysis by Cuijpers. A total number of 29 studies were found, with an average between-group (comparison with control condition) effect size of Cohen's d=0.77 and an average within-group effect size of d=1.20. A separate analysis was made between group-administered and "self-administered" (though still with guidance), yielding no difference in effect (d=0.99 and d=0.98 respectively).

In yet another, more recent, meta-analysis on self-help studies for depression including 34 studies, Gellatly and co-workers (2007) showed that studies with higher efficacy were those that to a higher degree used observer-rated outcome measures, recruited participants from non-clinical settings but with a diagnosis of depression (and not purely prevention of depressive symptoms), and who included contact with a therapist (guided self-help). However, of these factors, only guidance showed to be statistically significant in the multivariate analysis.

In a meta-analysis on bibliotherapy by Gould and Clum (1993), including 40 studies of a wide range of different target problems, an average between-group effect size of Cohen's d=0.76 was found at post-treatment, and d=0.53 at follow-up. The average effect-size for the 8 studies evaluating interventions of "fear reduction" (5 of them explicitly targeting "phobia or panic disorder") was 1.11. Moreover, in a comparison of "pure" self-help versus self-help with minimal therapist contact, no significant differences were found. It is however difficult to judge this finding, since information was somewhat scarce on the exact nature and amount of contact with a professional that still was a part of the "pure" self-help studies (as "assessment").

Another meta-analysis published by den Boer and co-workers (2004) including 14 studies of mood- (9 studies) and anxiety disorders (4 studies; with one study of mixed anxiety/depression) showed an average between-group effect size (comparisons with control/wait-list) of d=0.84 at post-treatment and d=0.76 at follow-up.

Summing up, there is a relatively solid evidence base for bibliotherapy for depression as well as for PD, at least when it is guided by a therapist. However, the exact contribution of therapist guidance specifically versus treatment structure more generally (careful in-person assessment before and after treatment etc) is not well elucidated. In a recent trial on PD it was shown that even unsupported bibliotherapy was effective, when accompanied by a clear deadline of treatment completion (Nordin, Carlbring, Cuijpers, & Andersson, 2010)

1.4.2 Internet-based treatment

Thus, we know of efficacious psychological treatments for depression and PD, but these treatments have a relatively low degree of access. We also know that self-help approaches may be one solution to the problem of dissemination and accessibility.

However, despite that there is evidence for the efficacy of guided self-help approaches since at least 30 years back, they have to a large degree been neglected within health care (den Boer, et al., 2004). Thus, as indicated earlier, they have not managed to significantly improve access for patients to empirically supported psychological treatments.

The advent of computers and the Internet may have come to provide a solution to this problem, by providing new, more efficient ways of delivering self-help programmes as well as brief therapist contact (Hohl, Berger, Bergström, Andersson, & Caspar, 2010). As will be outlined below, Internet treatment provides an integrated structure for the combined deliverance of self-help material and therapist contact, that may more easily be disseminated within the health care system than printed books, manuals and in-person therapist guidance (Andersson, 2009).

1.4.2.1 Computers, Internet and psychotherapy

The idea of using modern technology in psychotherapy and in the treatment of psychiatric problems is not new. An early example of the use of computers in this area was ELIZA, a computer programme conceived by Joseph Weizenbaum (1966), that could emulate responses in the manner of a non-directive Rogerian psychotherapist. This early, partly parodical, example was in other words aimed at substituting the therapist, that is, the patient being only in interaction with a programme.

ELIZA actually points to a fundamental difference in the stance taken by different researchers in the area of computerised or Internet-based treatment ever since. This difference basically reads: the technology developed, is it there to *substitute* the therapist or to *complement* him or her? Or rephrased in line with the discussion raised above: is the developmental goal a self-administered treatment or is it a minimal-contact/guided-self-help treatment? The impact of these questions will be elucidated below.

Following a rise of interest in the general use of computers in psychiatry in the 1970s (Klein, Greist, & Van Cura, 1975), in the early 1980s researchers increasingly started to investigate computerised assessment for psychiatric patients with for instance anxiety (Carr & Ghosh, 1983). The step to psychological treatment was then not far for researchers within the behavioural bibliotherapy tradition. Isaac Marks and co-workers developed a treatment of "self-exposure" for agoraphobia not only in book- but also in computer form (Ghosh, Marks, & Carr, 1984). In this early example of what was later to be called computerised cognitive behaviour therapy (CCBT) (Baer, Greist, & Marks, 2007) one already finds the idea of therapist substitution where "the computer was programmed to 'discuss' exposure tasks" (Ghosh, et al., 1984). However, in the subsequent randomised trial that found support for efficacy, all patients actually did see a clinician before and after treatment, during which all participants also had minimal therapist contact (Ghosh, Marks, & Carr, 1988).

The work by Marks and co-workers engendered the development of several interactive applications for stand-alone computers and for CD-ROMs, like "Fear Fighter" (Kenwright, Liness, & Marks, 2001) for anxiety and "Beating the Blues" (Proudfoot, et al., 2004) for anxiety and depression, both showing efficacy in reducing phobic and depressive symptoms respectively. These programmes were also, as their somewhat "catchy" names may reveal, commercial products.

However, in the mid 1990s the advent of the Internet changed, among many things, the role of computers. If the primary goal of the computer user previously was to interact with computer programmes, even so elaborate, since the advent of the Internet the primary goal of the user is to interact with the world, that is, largely with other people – personally as well as professionally. This also changed the area of computer assisted psychological treatment, partly shifting the focus from (self administered) interactive computer programmes to Internet based self-help applications with integrated minimal therapist contact (Andersson & Carlbring, 2003).

However, many conceptual confusions (and controversies) still surround the area of computer- and Internet based CBT. While some follow the example of ELIZA, like Marks and co-workers (2007), and holds that the very *raison d'être* of these interventions is largely to delegate the unique function of the therapist to the computer or Internet application, others, like our group (Andersson, Bergström, et al., 2008) hold that this is not necessary or even desirable. In our perspective, what is important is not the technology per se but the over-arching goal of enhancing access to psychological treatments, made possible by the significant reduction in therapist time when using guided self-help (Andersson, 2009), even when using technologically simple self-help applications. That is, the fact that more elaborate interactive computer programmes seek to emulate therapist functions, like decision making or therapist feedback, does not necessarily enhance neither treatment effect nor cost effectiveness. These technologically advanced programmes also often need commercial involvement for their development to be possible, raising several additional problems, namely the sometimes conflicting interests between commercial and scientific enterprise (Rosen, 1987).

The studies in this thesis are thus trials of *Internet*-based psychological treatments, and the review of previous treatment outcome research below will focus on studies in this line of work (rather than on computerised stand-alone programmes). This also reflects the development in the field, where evaluations of non-Internet-based computerised applications are increasingly scarce in the research literature in comparison with Internet-based treatments.

1.4.2.2 Treatment outcome

1.4.2.2.1 Panic Disorder

Internet-based guided-self help has been shown to be efficacious for anxiety disorders (Andersson, Bergström, Carlbring, & Lindefors, 2005), and more specifically for PD (Richards, Klein, & Carlbring, 2003).

In an early randomised trial, Carlbring and co-workers (2001) evaluated Internet guided CBT-self-help for PD for the first time, by comparing it to a wait-list control condition. Participants received information about the trial through newspaper articles and could then apply to participate on a web-page. There they were filled out a web-based self-diagnostic tool called the CIDI-SF (Kessler, Andrews, Mroczek, Ustun, & Wittchen, 1998), and several self-rated questionnaires. No in-person interview was thus performed. The self-help programme consisted of six modules presenting well-known CBT principles; psychoeducation, breathing retraining, cognitive restructuring, interoceptive- and in-vivo exposure, and relapse prevention. Participants were guided through treatment by weekly brief e-mail contact with a therapist, who provided access to subsequent modules in a stepped fashion. 41 participants were randomised to either such Internet CBT or to a waiting list, and at post-treatment those in the treatment condition had improved significantly on self-report measures related to panic- and agoraphobic symptoms whereas participants in the control had not improved. However, no long-term follow-up was made, and PD diagnosis was thus determined by self-report, and not in a clinical interview.

To adequately obtain diagnosis, in-person clinical interviews were performed in a subsequent study (Carlbring, Ekselius, & Andersson, 2003). In this trial the aim was to examine the importance of the amount of therapist contact in Internet treatment, while comparing it to another evidence based treatment for PD, namely AR (Öst, 1987), adapted to an Internet format. The same CBT self-help programme as in the first trial was used. The results in the this study showed that, although not statistically significant, the AR treatment had larger ES than the Internet CBT (Cohen's d=0.71 for AR and d=0.42 for CBT), probably because of the reduction in amount of guidance provided in this trial relative to the previous one. However, compliance to the treatment judged being a problem, in yet another study by the same group (Carlbring, et al., 2006) weekly telephone calls were added to Internet treatment (still including the same format with self-help, guided by therapist e-mail support) which resulted in better compliance and better, larger ES (with an average of Cohen's d=1.2 on measures of anxiety and agoraphobic avoidance). Treatment effects were sustained at 9-months follow-up. In yet another recent open trial, the programme by Carlbring was evaluated in a

community setting in Norway (Nordgreen, et al., 2010) where 27 participants diagnosed with PD in an in-person diagnostic interview were eventually included. The average within-group effect size on panic- and agoraphobic questionnaires at post-treatment was Cohen's d=0.65 and at the 6-month follow-up it was d=0.50. The drop-out rate was somewhat larger than in the earlier randomised studies. An analysis of predictors of outcome was also made in this trial that showed that a longer duration of PD was related to worse outcome.

Study III, using a modified version of the programme developed by Carlbring, can be said to be a first open effectiveness evaluation in a regular clinical environment, complementing these earlier efficacy trials with self-recruited participants by Carlbring and co-workers. The importance of effectiveness (as opposed to efficacy) research will be elucidated below (1.5.1)

In one trial by a British group (Schneider, Mataix-Cols, Marks, & Bachofen, 2005) the effect of two different Internet-administered programmes were compared for "phobic and panic disorders". Thus participants were not exclusively PD-sufferers, and participants with social- and specific phobia were also included. Participants were, after an assessment interview by telephone, randomly assigned to receive either a 10-week exposure-based CBT programme ("Fearfighter") or an equally 10-week long non exposure-based "minimal" CBT programme. Therapist support was given by telephone calls. After treatment both conditions showed significant and similar improvement. After a short 1-month follow-up, improvement was significantly greater in the exposure condition on half of the phobic-related self-report measures. In a very small open study by the same group (Kenwright, Marks, Gega, & Mataix-Cols, 2004), ten participants accessed the Fearfighter programme from home via the Internet, and improved significantly on self-report of phobic symptom severity.

In two trials directly comparing Internet CBT with individual face to face CBT, these treatment formats were found to be equally efficacious (Carlbring, et al., 2005; Kiropoulos, et al., 2008). In the study by Carlbring and co-workers (2005) 49 participants were after an in-person SCID-interview randomised to either 10 individual CBT sessions or 10 weeks of Internet CBT. The within-group ES at the 1-year follow-up was Cohen's d=0.80 for Internet CBT and d=0.93 for individual face-to-face CBT. In a subsequent study on predictors of treatment outcome on participants in this study (Andersson, Carlbring, & Grimlund, 2008) it was found that, in line with earlier research on predictors of outcome in traditionally administered CBT (Ramnerö & Öst, 2004), agoraphobic avoidance at baseline was the strongest negative predictor of outcome. However, this was not the case for the Internet treatment. The authors hold that this can possibly be explained by the fact that the need of coming to a clinic in traditional CBT constitutes a too brusque agoraphobic exposure that may interfere with subsequent treatment, while participants in Internet CBT had an initially "smoother" encounter with treatment, which would allow them to subsequently profit more from it.

Study IV, following Study III, can be seen as an effectiveness trial building directly on this efficacy trial of Carlbring and co-workers (2005) by comparing Internet CBT with live, group CBT in a psychiatric setting with predominantly referred patients.

In the trial by Kiropoulos and co-workers (2008) the 86 participants were, after an in-person ADIS-IV-interview, randomised to either a 12 week Internet CBT-treatment called "Panic Online" or to a "gold standard" face-to-face CBT (Barlow & Craske, 2000). At post-treatment 30.4% of the participants in the Internet CBT-condition and 27.5% in the face-to-face condition achieved high end-state functioning. No long-term follow-up measurement was made in this trial. The same research group later examined, in a randomised trial, the importance of therapist competence (Shandley, et al., 2008). The same Internet CBT-programme was used in both conditions, but the e-mail support was given either by clinical psychologists (n=43) or the patients general practitioner (GP; n=53), having received brief CBT training. No significant differences between the two treatment conditions were found at neither post-treatment or at the 6-month follow-up on measurements of panic and related symptoms. However, attrition was fairly high, and more patients dropped out to post-treatment in the GP condition than in the psychologist condition, the latter also having a statistically significant larger improvement on two quality of life-subscales.

1.4.2.2.2 Depression

A relatively large number of trials have evaluated Internet-based CBT for depression, but compared to the literature on PD, there are much larger conceptual and methodological differences across studies. In a meta-analysis by Andersson and Cuijpers (2009a) on Internet- or computerised CBT for depression an overall between-group (comparison with control) effect size of d = 0.41 was found. However, a significant difference was found between those interventions providing therapist support (d=0.61) and those not providing support (d=0.25), which is in line with a previous meta-analysis (Spek, Cuijpers, et al., 2007).

In several trials covered in this meta-analysis an in-person diagnostic clinical interview has not been used. As in Study I, assessment was instead carried out by way of online forms. The only Internet-based study that did include an in-person interview was conducted by Spek and co-workers (2007), targeting sub threshold depressive symptoms in people over 50 years of age. In this study, after this clinical interview establishing diagnosis, participants were randomised to either Internet CBT (however without therapist support), CBT group treatment (Lewinsohn, et al., 1984) or to a wait-list group. Both active treatment conditions were significantly more effective in reducing sub threshold depressive symptoms than the waiting-list, results which were maintained for the Internet CBT but only partially for the group CBT at 12-month follow-up (Spek, Cuijpers, et al., 2008). In a subsequent study analysing predictors of treatment outcome, high pre-treatment depression scores, female sex and less neurotic personality traits were associated with better treatment outcome in both Internet- and group treatment (Spek, Nyklicek, Cuijpers, & Pop, 2008).

In a study by Warmerdam and co-workers (2008), included in the meta-analysis mentioned earlier, Internet-based CBT was compared to Internet-based problem solving therapy (PST) and a wait-list control condition. Participants were recruited through media and no in-person assessment was made. The 8-week CBT self-help programme was based on behavioural principles (Lewinsohn, et al., 1984) and the 5-week PST programme was based on self-examination bibliotherapy as developed by

Bowman (1995). Participants received both automated as well as personal e-mail feedback from therapists, amounting to a total of 100 minutes for PST and 160 minutes for CBT. Despite a fairly elevated drop out rate and no long-term follow-up, the study provided some evidence for treatment efficacy, when 12-weeks after baseline both treatment groups showed medium effect sizes on measures of depressive symptoms compared to wait-list (CBT: Cohen's d = 0.72, PST: Cohen's d = 0.66)

In another trial covered in the meta-analysis by the same Dutch group (van Straten, Cuijpers, & Smits, 2008), an Internet-self help programme (with e-mail support) based on problem solving therapy was compared with a wait-list control condition, for participants with depressive and anxiety symptoms as well as work-related stress. Post-treatment data obtained from 83% of the participants showed that the intervention group had improved significantly more than those in the control group on measures of depressive symptoms.

As mentioned, in many studies on Internet CBT for depression, including several of those included in the meta-analysis by Andersson and Cuijpers, no formal diagnostic procedure is performed, and in some no therapist contact is established neither. The results from such "open access" interventions shows that they are only to a small degree, or not at all, more effective than psychoeducation only (Christensen, Griffiths, & Jorm, 2004; Christensen, Griffiths, Mackinnon, & Brittliffe, 2006; Mackinnon, Griffiths, & Christensen, 2008; Patten, 2003). Because of high attrition rates in these studies, it is difficult to draw well-founded conclusions. In the results from two other studies, included in Andersson and Cuijpers meta-analysis, the relation between therapist guidance and efficacy became especially clear, the first trial with no support not achieving significant reduction in depressive symptoms (Clarke, et al., 2002), whereas once support was introduced, the intervention did show effect (Clarke, et al., 2005). A third trial by the same group (Clarke, et al., 2009), again comparing pure (unguided) Internet self-help with a treatment as usual condition, yielded a small between group effect size (Cohen's d=0.20)

From a broader public health perspective it may however be unfair to criticise open-access interventions for their high attrition and generally low effects, since their aim have not been to deliver specific psychiatric treatment to diagnosed patients, but rather to be a tool for the prevention of depression and anxiety in the community (Andersson, 2009). In this perspective, high-rates of attrition is probably inevitable and may not be contradictory to its goal of providing broad community health prevention services.

There are a number of more recent trials on Internet CBT for depression not included in Anderssons and Cuijpers meta-analysis worth mentioning because they show promising results.

In a large trial conducted within the general practice health care system in Great Britain by Kessler and co-workers (2009) an online, real-time CBT intervention (thus not guided self-help) was compared to usual care by a general practitioner. In this trial, an in-person assessment of diagnosis and symptom severity was made, followed by 10 55-minute sessions of online text-based interaction with a therapist. After treatment, the amount of patients recovered from depression was significantly higher in the treatment

group (38%) than in the usual care control group (23%), which also was retained at the 8-month follow-up (42% and 26% respectively).

In a second recent trial not included in the mentioned meta-analysis, Jeroen Ruwaard and co-workers (2009) randomised 54 participants with moderate depression to either Internet CBT or a wait-list control condition. The Internet CBT consisted of a web-based self-help programme that was accompanied by e-mail support by a therapist and thus resembled the treatment of Study I. However, it was both longer (on average 16 weeks) and included considerably more therapist time (on average more than 7 hours per therapist and patient) than in Study I. Participants were recruited through information in a newspaper. No in-person diagnostic procedure was performed, and assessment was based solely on self-report. At post-treatment, while the control group also got better, improvement was greater in the treatment condition, with an between-group effect size of Cohen's d=0.9 (depression measures pooled together) and gains were maintained at the 18-month follow-up, when the control group also had received treatment. In this trial potential predictors of outcome were also examined, and besides the methodologically expected positive correlation between pre-treatment depression severity and post-treatment improvement, the only (negative) correlation found was between presence of antidepressant pharmacological treatment and improvement at follow-up.

In a third recent trial (Meyer, et al., 2009) an open Internet-based treatment package including CBT-principles was found to be efficacious for participants recruited from depression discussion groups on the Internet. Even though no therapist support was given, attrition was "only" 45%, possibly because there was a clear treatment structure with deadline for treatment completion (Nordin, et al., 2010) and participants had scheduled interactions, however automated by the programme.

In a fourth large study by de Graaf and co-workers (2009), not included in the previously mentioned meta-analysis, 303 participants recruited from the community were, after computerised assessment and self-diagnostics, randomised to either Internet CBT (without therapist support), treatment as usual (TAU) in a general practitioner (GP) setting, or TAU + Internet CBT. The Internet CBT programme was a Dutch adaptation of the previously mentioned Coping With Depression course by Lewinsohn. TAU included GP appointments and pharmacological treatment when indicated. Up to a 6-month follow-up, dropout was only 9.2% in this large sample. At the 6-month follow up, all conditions improved, showing within group effect sizes of Cohen's d=0.86, d=0.81 and 0.89 respectively. However, between group effect sizes were near zero, and thus no significant differences were found between conditions. The authors conclude that the fact that no guidance was given probably accounts for the relatively moderate effect, and that there was no superiority of CBT over TAU.

Finally, recently an Australian trial was published (Perini, Titov, & Andrews, 2009) which in its design is much more similar to Study I than the previously reviewed studies. In this trial participants were recruited through a website where an automated screening was made. Followed a telephone-interview that established diagnosis of depression by way of MINI (Sheehan, et al., 1998). A total of 45 participants met all inclusion criteria and were randomly assigned to either Internet guided self-help or to a

waitlist control condition. The 9-week Internet CBT consisted of 6 modules, homework assignments, participation in a discussion group, and obligatory e-mail contact with the therapist. The average therapist time used per patient during treatment was 111 minutes. No follow-up measurement was made in this trial, but at least at post-treatment the intervention was shown to be effective, with an within-group effect size on the BDI of Cohen's d=1.15 and a between-group effect size on the same measure of d=0.63.

Yet two more trials by our group have evaluated a revised version of the treatment programme (Andersson, Bergström, Holländare, Lenndin, & Vernmark, 2007) that first was developed for Study I. In the first one (Vernmark, et al., 2010), the guided self-help programme (n=29) was compared to individualised e-mail therapy (n=30) and to an untreated wait-list condition (n=29). Drop-out rate was low, with 84% providing both post-treatment and 6-month follow-up assessments. As mentioned, the model of guided self-help was equivalent to the one used in Study I. The content of the e-mail therapy overlapped substantially with the self-help used in this condition, but the possibility of individualisation from the therapist was larger, both in terms of feedback given and in terms of home-work assignments. A specific therapist manual was developed for this purpose. Average therapist time spent per participant was 53 (SD= 28) minutes in the guided self-help condition and 509 minutes (SD = 176) in the e-mail therapy condition. No significant differences in treatment outcome were found between the two active treatments neither at post-treatment nor at follow-up and both were superior to the waiting-list control group. However, individualised e-mail therapy demanded nearly 10 times more therapist time than did the guided self-help treatment, the latter thus being more cost-effective.

Relapse is unfortunately a common problem after discontinued treatment, not only after pharmacological but also after cognitive behavioural treatment (Vittengl, et al., 2007). In the second study by our group using a revised version of the programme developed for Study I, the guided self-help format was used in a trial to prevent relapse in depression (Holländare, Johnsson, et al., 2010). After recruiting participants through newspapers, participants went through a telephone interview based on the SCID-I (First, Gibbon, Spitzer, & Williams, 1996). The inclusion criteria were that the participant must have had at least one major depressive episode (MDE) during the last five years, but not currently be fulfilling criteria for an MDE. Moreover, participants had to have residual mild depressive symptoms, as defined by having a score of between 7 and 19 on the Montgomery Åsberg Depression Rating Scale – Self-rated (MADRS-S) (Holländare, Andersson, & Engström, 2010; Holländare, Askerlund, Nieminen, & Engström, 2008; Svanborg & Åsberg, 2001). After inclusion participants were randomised to either Internet CBT (n=38) or to a wait-list control group (n=39) for 10 weeks. Results showed that, in the Internet CBT group no participant relapsed during the 10 weeks of treatment, whereas in the control condition, 10 participants relapsed (25.6 %) during this time. This difference between the groups was statistically significant. However, no significant difference was seen in the reduction of depressive symptoms as measured by the BDI or MADRS-S. At six months after the intervention, there was still a significant difference in relapse rates between conditions, but again, no significant differences in levels of depressive symptoms. The latter finding is possibly due to low power and a statistical "floor effect" since these participants, having

recovered from a MDE, had relatively low symptoms levels. This was the first study to show that an Internet CBT intervention for depression may prevent relapse in a MDE. It is an area that merits further research attention.

In conclusion these two studies, building upon the programme developed for Study I, both replicates this study's findings and shows that adding considerably more therapist time does not enhance treatment outcome. Moreover, it gives tentative evidence that Internet-based CBT is effective in reducing relapse rates in depression.

1.5 FROM DEVELOPMENT TO DEPLOYMENT

1.5.1 Efficacy and effectiveness

Treatment outcome research, and the field of guided self-help and Internet treatment is no exception, can be construed as having three essential steps; efficacy, effectiveness and implementation or dissemination (Schoenwald & Hoagwood, 2001). One could argue that, up to until recently, treatment outcome trials have almost exclusively been those of establishing efficacy, as evident in the field of Internet-based treatment by the review of outcome studies made above. The dominant line of research has thus been the evaluation of treatments in carefully controlled settings with selected (usually self-recruited) participants, forming the Empirically Supported Treatment (EST) (Chambless & Hollon, 1998; Lutz, 2003). Evaluations of such ESTs treatments in "usual care" settings have largely been lacking. This in turn has evoked much criticism within the research literature, many claiming that ESTs do not tell us anything about "real life" psychological treatment (Shadish, Matt, Navarro, & Phillips, 2000).

Recent years have however seen a strong gain in the interest for effectiveness research (Hoagwood, Hibbs, Brent, & Jensen, 1995) while dissemination research, that is the study of which practices should be adopted to reach the goal of actual deployment in usual-care services, is within the field of psychological treatment still in its very infancy (Garland, Hurlburt, Brookman-Frazee, Taylor, & Accurso, 2009).

While the goal within efficacy research is to maximise internal validity, that is the degree to which one can determine the causal factors involved in the observed change during treatment, the goal within effectiveness research is rather to maximise external validity, that is the degree to which the results are representative for usual care contexts (Stewart & Chambless, 2009). Of course there is no absolute and mutually exclusive distinction between efficacy- and effectiveness research, but rather a continuum between the poles of maximum internal- and external validity. In effectiveness trials patients are preferably referred in a regular manner to treatment (and not solicited by the researcher), extensive exclusion criteria are not used, those performing treatment should preferably be regular staff not specially trained for participation in the trial and the patients in the trial should not receive more special attention or additional treatment interventions in comparison to what patients normally would receive (Shadish, et al., 1997).

In a meta-analysis by Shadish and co-workers (2000) 90 effectiveness studies of psychotherapy were included and the main conclusion was that therapies are effective over a large range of clinical settings, with medium to large effect sizes. Effects were shown to increase with larger therapy dose and when outcome measures are specific to treatment.

In a more recent meta-analysis that included subsequent studies carried out in clinically representative settings but not covered by the meta-analysis by Shadish, Stewart and Chambless (2009) included 56 published effectiveness trials of CBT for anxiety disorders. In this meta-analysis the average within-group effect size for studies measuring PD symptoms was Cohen's d=1.02.

1.5.2 Cost-effectiveness

Another aspect of clinical research receiving increasing amount of attention in the literature is cost-effectiveness analysis (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005). In the light of the issues of dissemination and accessibility of psychological treatments raised above, formal evaluations of the relation between costs of treatment delivery and effects of treatment are crucial.

The basic principle of cost-effectiveness analysis is to relate costs to effectiveness and to thus obtain a cost-effectiveness ratio. More specifically, one uses the term incremental cost-effectiveness ratio (ICER) (Wang & Zhao, 2006) which is a measure of the additional cost of a new treatment (compared to an alternative, or no treatment) for each additional unit of effectiveness. The measurement in effect is in these types of analysis often made in so-called quality-adjusted life years (QALYs) (Broome, 1993), but can also be any measure of effect, such as in Study IV, were the clinician rated measure PDSS (Shear, et al., 1997) was used for this purpose.

The cost-effectiveness of computer- or Internet-based treatment is not well known (Kaltenthaler, et al., 2006; Palmqvist, Carlbring, & Andersson, 2007), which also has been specifically pointed out by SBU, The Swedish Council on Health Technology Assessment, in a report on the evidence of computerised and Internet-based CBT (Linton, 2007). However, in a promising first study by McCrone and co-workers (2004) of the computerised CBT programme "Beating the Blues" for anxiety and depression discussed earlier, a high probability of the intervention to be cost-effective was found, even when a low monetary value was set to each unit of symptom improvement.

1.5.3 Development of studies in the thesis

As already touched upon, this thesis reflects the move that research on computerised and Internet-based guided self-help has taken during the latest 10 years, shifting focus from purely efficacy research to also incorporating the themes of effectiveness, cost-effectiveness and implementation in regular care.

In Study I, being an early trial, the aim of the study was to examine the efficacy of Internet-based CBT for depression, comparing it with a condition of receiving only participation in a discussion forum, but no treatment. It was thus not carried out in a psychiatric setting and the participants treated for depressive symptoms were neither referred patients nor accessed in a regular clinical interview.

Study II examined predictors of outcome in patients from Study I.

In Study III, being a later study conducted after the efficacy of Internet-based CBT for PD had already been established in numerous trials as reviewed above, the aim was to evaluate Internet-based CBT for PD in a regular psychiatric setting with patients referred for treatment and not recruited by advertisement. The study represents a transition into the psychiatric milieu with the introduction of rigorous psychiatric diagnostic assessment and also constitutes a feasibility study, examining how Internet-based treatment could be integrated in a psychiatric environment.

In the much larger Study IV, that followed Study III, the primary aim was to compare the effectiveness of Internet-based CBT with group CBT for PD, in a psychiatric setting with referred patients. This was the first time this was done in a RCT for *any* psychiatric disorder. Such a move into the domain of effectiveness research is important, if the step into real-life implementation of novel treatments is to be made, and thus if the goal of guided self-help and Internet treatment is truly to be achieved – that is, that of making evidence based psychological treatment accessible to a much larger number of people. The secondary aim of Study IV was to evaluate and to compare the cost-effectiveness of Internet- and group treatment.

Studies I through IV are outlined below.

2 THE EMPIRICAL STUDIES

2.1 STUDY I. INTERNET-BASED SELF-HELP FOR DEPRESSION: A RANDOMISED CONTROLLED TRIAL

2.1.1 Aims

The aim of this study (Andersson, Bergström, Holländare, et al., 2005) was to investigate the effects on depressive symptoms of Internet-based CBT (self-help with short e-mail support) including participation in a monitored discussion group, compared with participation in the discussion group only (Houston, Cooper, & Ford, 2002).

2.1.2 Methods

Participants were recruited through a press release and subsequent articles in Swedish newspapers which included the address of a website that provided general information and instructions on how to proceed to complete a computerised version of the Composite International Diagnostic Interview Short-Form (CIDI–SF) (Kessler, et al., 1998) which renders a diagnosis of major depression and other main comorbid diagnoses.

Participants also completed the Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and the MADRS–S (Montgomery & Åsberg, 1979) on the website. Besides depression self-ratings participants completed a form requesting their e-mail address, information on their age, gender, the size of town in which they lived, the three first digits of their postal code (to obtain an estimation of geographical spread within Sweden), education, occupation, medication and contacts with healthcare professionals.

To be included in the trial, the participants had to have a probability of 55% or more for the diagnosis of major depression (on the CIDI-SF), have a total score on the MADRS-S between 15 and 30 (mild-to-moderate depression; including a score of less than 4 on item 9 - zest for life), not suffer from psychosis (according to medication status) nor bipolar disorder, not having begun antidepressant medication within one month prior to start of the trial (or changed in dosage during that time), not have a history of cognitive–behavioural therapy for depression, be 18 years or older, be prepared to work with the self-help programme several hours each week, and have had completed pre-treatment assessment. Participants were then randomised by an independent person by way of a random number procedure.

The principal outcome measure of depression was the 21-item BDI (Beck, et al., 1961) and the results are based upon this instrument. Besides the MADRS-S (9 items), the 21-item Beck Anxiety Inventory (BAI) (Beck, Epstein, Brown, & Steer, 1988) and the Quality of Life Inventory (QOLI) (Frisch, Cornell, Villanueva, & Retzlaff, 1992) were

also administered. The cognitive–behavioural self-help programme was based on Beck's CT, as presented in the self-help book "Feeling good" (Burns, 1999), and on behavioural activation (BA) as presented in the self-help book "Control your depression" (Lewinsohn, et al., 1986) and in the book "Depression in context" (Martell, et al., 2001). The material (presented in Swedish) consisted of 89 pages of text, divided into five modules: introduction; behavioural activation; cognitive restructuring; sleep and physical health; and relapse prevention and future goals. The sleep module was based on a programme for insomnia (Ström, Pettersson, & Andersson, 2004). The amount of time advised for completion of all five modules was 8 weeks. However, the mean time for completion was 10 weeks. The therapist time spent on each participant was estimated to be 2 hours in total, including screening, responding to e-mails and monitoring the discussion group.

For ethical reasons the control group participants were given access to the treatment modules after the intervention group had finished their treatment. Participants were contacted by e-mail and asked to fill in the questionnaires again on the internet 6 months after the treatment had ended. All randomised participants with follow-up data were included in the analyses regardless of how many treatment modules they had completed. This could also be referred to as 'intention to treat', as we included all those who provided post-treatment data. However, for the main outcome measure we also calculated results on a last observation carried forward basis, replacing missing values post-treatment with pre-treatment values.

Of the 343 persons who completed the inclusion forms, 117 (34%) were included; 226 persons were excluded from the study. The most common reason for exclusion was risk of suicide (n=77; measured by item 9 on the MADRS-S) and not being mildly-to-moderately depressed (n=67; measured by total MADRS-S score).

2.1.3 Results

Post-treatment measures were completed by 36 participants in the treatment group and 49 in the control group. These 85 participants were included in all statistical analyses regardless of the amount of treatment received. In total the rate of withdrawal from the treatment was 27% (32 of 117).

Analyses of variance with a 2x2 design (one group factor and one repeated-measures factor) resulted in significant interactions for the BDI ($F(1,83)=14.22$; $p<0.001$), MADRS–S ($F(1,83)=7.77$; $p=0.007$) and BAI ($F(1,83)=5.72$; $p=0.019$). These interactions reflect differences in change scores between the active treatment and the control condition. The corresponding effect sizes (Cohen's d between groups at post-treatment) were 0.94 for the BDI, 0.79 for the MADRS–S and 0.47 for the BAI. Replacing missing values with the last observation available for the full sample of 117 participants did not alter the results on the main outcome measure BDI.

Participants in the intervention group normally reached at least the fourth module, with 65% completing all modules. The average number of modules completed was 3.7 (SD=1.9). The number of modules completed was negatively correlated with post-

treatment BDI scores (Spearman's r=–0.33, $p<0.05$). Activity in the discussion group was not correlated with improvement in the treatment group.

At the 6-month follow-up, all participants had received treatment and 71 of them (all in the treatment group and 35 in the control group) completed the questionnaires again, yielding a 16% rate of participants lost to follow-up from post-treatment (0% in the treatment group and 29% in the control group). Analysis of the difference between the groups at follow-up revealed no statistically significant difference. However, both groups demonstrated significant effects indicating that treatment gains were maintained to follow-up. As the control group also had received treatment, we expected changes between post-treatment and follow-up for this group, but no difference for the treatment group. This assumption was confirmed by means of paired t-tests for the BDI, MADRS–S, BAI and QOLI (all p values were less than .05 in the control group and more than .05 in the treatment group).

2.1.4 Discussion

This randomised controlled trial of Internet-delivered self-help with brief therapist support based on CBT yielded two major results. First, the active treatment, which included standard CT approaches and behavioural activation, resulted in decreased depressive symptoms immediately after treatment and at the 6-month follow-up. Benefits were also observed regarding anxiety symptoms and quality of life. Second, only participation in a web-based discussion group had no effect on depressive symptoms, which is in contrast with a study showing some benefits from participation in an Internet support group (Houston, et al., 2002).

There was a differential rate of withdrawal between the two groups, and judging from the comments we received, some perceived the text and the exercise as too demanding. A solution to this is to adjust the text, and to allow a longer treatment period. Although self-report was used to obtain a likely diagnosis using DSM criteria, no formal diagnosis was made in an interview. Hence, it is possible that people with depression were excluded and people without depression were included. However, this is not very likely, particularly the latter possibility of including people who would not fulfil DSM depression criteria in a structured interview. Research on Internet-based self-help for depression would benefit from clear-cut diagnoses before initiation of treatment; in our study, we did not use a clinician-administered interview.

2.2 STUDY II. DELIVERING CBT FOR DEPRESSION VIA THE INTERNET. PREDICTING OUTCOME AT 6-MONTHS FOLLOW-UP

2.2.1 Aims

In this study (Andersson, Bergström, Holländare, Ekselius, & Carlbring, 2004) we returned to Study I to analyse predictors of outcome at 6-month follow-up. This is crucial because it cannot be inferred that the same outcome predictors will be relevant in Internet based treatment and in face-to-face therapy.

2.2.2 Methods

See Study I for a more complete description of methods used in the randomised trial. In this study we used the data obtained at the 6 month follow up. In total, 71 participants completed the 6-month follow-up (84% of the original sample). Mean age of the participants was M=37 years (SD = 11), and there were 79% females.

As mentioned earlier in Study I the principle outcome measure of depression was the BDI (Beck, et al., 1961); in addition the MADRS-S (Mattila-Evenden, Svanborg, Gustavsson, & Åsberg, 1996; Montgomery & Åsberg, 1979) was administered. For predictor analyses, we calculated a change index of these two measures. In order to estimate if pre-treatment self-reported levels of depression, anxiety and quality of life were associated with outcome, we used pre-treatment scores from the BDI, MADRS-S, BAI (Beck, et al., 1988) and the QOLI (Frisch, et al., 1992). Other pre-treatment predictors were demographic and clinical data such as age, gender, education (in 5 categories), and number of episodes of depression before entering the trial.

Results were analysed by means of multiple regression analysis, entering predictor variables simultaneously. In addition, Pearson correlations and Spearman rank correlations were calculated when needed. Given the common practice of using correlation coefficients (raw) as estimates of effect size (Rosenthal, 1991), we decided to present results from regression analyses and raw correlations. For the first set of regression analyses, we used the change index as dependent variable and the demographic and clinical factors as predictors. For the second set we used follow-up levels of the BDI and MADRS as dependent variables and pre-treatment levels of these two questionnaires, of the BAI, and of the QOLI as predictor variables.

2.2.3 Results

The mean change score (e.g., improvement in raw scores from pre-treatment to follow-up) for the BDI was M = 7.7 (SD = 9.8), and M = 6.5 (SD = 8.7) for the MADRS-S.

For the BDI change score, the number of previous episodes of depression was associated with worse outcome. This was also confirmed in the regression analysis [t = –2.1, p < .05, beta = –0.25]. The latter correlation was also significant when using Spearman's signed rank correlation (rho = –0.24, p = .04). The other demographic and clinical factors included in the regression were not associated with the outcome (all p's > 0.24). The regression analysis for the MADRS-S change score did not result in any significant finding.

For the second set of analyses, the BDI follow-up score was used as dependent variable and pre-treatment scores as predictors. While the overall regression was statistically significant (p = .008), none of the predictor variables reached statistical significance on their own. A different picture was seen when the MADRS-S was used as dependent variable as QOLI [t = –2.1, p < .05, beta = –0.29], BAI and MADRS-S pre-treatment levels [t = 2.4, p < .05, beta = 0.29] were associated with outcome.

2.2.4 Discussion

The main result of this study was that only weak associations between different presumed predictors and outcome were found, with the exception of pre-treatment levels of depression, anxiety and quality of life. This finding was expected, since higher self-reported severity has previously been seen to be associated with poorer outcome (Hamilton & Dobson, 2002). Albeit weak, a statistically significant correlation was found in the same direction showing that more episodes of depression was associated with worse response to the guided self-help treatment.

There are, of course, several methodological issues that should be commented on. We only analysed few possible predictors and with a relatively low statistical power. In future studies, it would be interesting to investigate the predictive power of social support networks and to account in detail for medication, e.g. SSRIs. In the present study we only asked about medication in general which was unrelated to outcome. In addition to adopting a multivariate model approach, we investigated each possible predictor separately, but did not adopt a stepwise approach. The use of change scores as dependent variables has been questioned (Steketee & Chambless, 1992), although the alternative of using residual change scores has been questioned also as being less comprehensible from a clinical point of view. Another objection made by Steketee and Chambless (1992) was that analyses of outcome predictors often consist of 'fishing expeditions', without clear preconception of what to look for. Admittedly, the data in the present study was not collected bearing treatment outcome predictors in mind. Still, given the lack of knowledge in this field, we believe that exploratory analyses were justified.

2.3 STUDY III. AN OPEN STUDY OF THE EFFECTIVENESS OF INTERNET TREATMENT FOR PANIC DISORDER DELIVERED IN A PSYCHIATRIC SETTING

2.3.1 Aims

The aim of this study (Bergström, et al., 2009) was to conduct an effectiveness trial evaluating an Internet-based treatment (including brief therapist contact) for PD in a regular psychiatric setting with patients referred for treatment and not recruited by advertisement. The treatment was specifically developed and adapted for the hospital IT environment and therapists were clinical psychologists working with anxiety disorders. Moreover, psychiatrists diagnosed patients for treatment as part of their regular practice.

2.3.2 Methods

Patients with presumed PD referred to the Anxiety Disorders Program at the Psychiatry Center Karolinska, Stockholm, were assessed in an in-person clinical interview. Twenty consecutive patients meeting the inclusion criteria were included during the study period.

Within the frame of a regular psychiatric assessment, a structured clinical interview was performed using the MINI (Sheehan, et al., 1998) as well as an analysis of blood samples to rule out a possible physical aetiology of the anxiety symptoms (e.g. hyperthyroidism or anemia). To be included in the study, participants had to meet the following criteria: 1) fulfil the DSM-IV (American Psychiatric Association, 2000a) diagnosis of PD with or without agoraphobia 2) PD being the primary diagnosis, 3) if on medication for PD, the dosage had to be stable for 2 months before entering the study. Patients were not excluded on the basis of comorbid axis I or axis II diagnosis, as long as the PD was considered the primary diagnosis. All patients were recruited through referrals.

The self-help programme was divided into 10 modules, delivered during a 10-week treatment phase. The programme consisted of five broader themes: psychoeducation, cognitive restructuring, interoceptive and in vivo exposure, and relapse prevention. Each patient was required to complete a module to get access to the following one after e-mail interaction with the therapist. Each feedback required approximately 5-10 min of the therapist's time. The treatment modules overlap in part with the programme developed by Carlbring and co-workers (2001), but some content as well as the sequencing of modules was slightly different.

The first main outcome measure in the study was the Panic Disorder Severity Scale (PDSS) (Shear, et al., 1997), which is a clinician-administered instrument assessing the number of panic attacks, limited symptom attacks, agoraphobic avoidance, somatic sensitivity and PD-specific effects on global functioning. Treatment response was defined as the proportion of patients showing at least a 40% decrease from baseline on the PDSS, as in conjuncture with earlier trials on PD (Barlow, et al., 2000; Milrod, et al., 2007).

The second main outcome measure was the self-report measure Mobility Inventory for agoraphobia (MI) (Chambless, Caputo, Jasin, Gracely, & Williams, 1985). Other self-report measures were the Beck Anxiety Inventory (BAI) (Beck, et al., 1988), Beck Depression Inventory (BDI) (Beck, et al., 1961), Montgomery-Åsberg Depression Rating Scale—Self-rated (MADRS-S) (Svanborg & Åsberg, 2001), and the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). All measures were obtained at pre-, post-treatment and at follow-up, with the exception of the HADS, which also was completed in association with each module.

Of the 20 consecutive patients included in the study, nine were men and 11 were women. Mean age was M=34 years (SD=7.0). Two patients dropped out before post-treatment and yet another before the 6-month follow-up. Outcome data were included in the statistical analysis regardless of the amount of treatment received, on an intention-to-treat basis (Newell, 1992).

2.3.3 Results

Using last observation carried forward (LOCF), all 20 patients were included in the statistical analyses. Following the procedures recommended by Rosenthal & Rosnow (1991), we calculated composite scores for the main outcome measures (e.g. PDSS and MI scales) by converting to Z-scores for each measure and then calculating the mean for this composite score.

A repeated-measure analysis of variance (ANOVA) showed a significant repeated-measures effect [$F(2,38)=22.2$, $p<0.0001$], which was followed by Bonferroni corrected t-test showing a decrease from pre- to post-treatment ($p<0.0001$), and between pre-treatment and follow-up ($p<0.0001$). There was no statistically significant change between post-treatment and follow-up. For the individual outcome measures dealing with PD the same outcome was obtained with main effects of time and post-hoc Bonferroni-corrected t-tests showing reductions on the PDSS and on the MI-scales (all $p<0.001$).

Using the criteria for treatment response (i.e. the proportion of patients showing at least a 40% drop from baseline on the PDSS), the proportion of responders (still on an LOCF-basis) was 75% at post-treatment and 70% at 6-month follow-up.

The secondary outcome measures showed repeated-measures effects for the BAI [$F(2,38)=15.0$, $p<.0001$], the HADS scales of anxiety [$F(2,38)=26.7$, $p<.0001$] and depression [$F(2,38)=14.01$, $p<.0001$], MADRS [$F(2,38)=10.3$, $p<.0001$], and finally

for the BDI [$F(2,38)=11.4$, $p<.0001$]. All post-hoc tests showed the expected result of a reduction between pre- and post-treatment, and between pre-treatment and follow-up.

The mean number of modules completed (out of 10 in total) for all 20 patients were 7.8 (SD=2.4) within the intended 10-week time frame. The average therapist time spent per patient and week was 11.4 min.

2.3.4 Discussion

The results of the present study suggest that Internet-based treatment within regular psychiatric care is effective for patients with PD referred from primary care and psychiatric outpatient settings. Both clinician- and self-rated measures showed significant improvements on PD-related symptoms as well as comorbid depressive symptoms.

Clinical trials showing the efficacy of CBT-based interventions are sometimes criticized for having too strict inclusion criteria and for treating less severe patients (for example less agoraphobic patients with little or no comorbidity as well as relatively short clinical history) in highly specialized university settings (Westen, Novotny, & Thompson-Brenner, 2004). This study evaluated Internet-based CBT within a regular psychiatric setting with consecutive referred patients, all of them agoraphobic with a mean clinical history of PD of several years. Twenty-five per cent of patients had at least one comorbid anxiety disorder and 20% had comorbid depression. Moreover, 70% of patients were on medication for their anxiety and/or depression. Therefore, we believe that our sample is in several important aspects representative of a clinical PD population within a regular care setting.

An obvious weakness of the study was that there was no control condition. However, earlier studies (Carlbring, et al., 2006; Carlbring, et al., 2001) have shown that the control group only shows a negligible change in panic and anxiety symptoms from pre- to post-test. The within group effect sizes observed in the present study are in line with those shown in earlier studies of Internet-based treatment of PD (Spek, Cuijpers, et al., 2007) as well as those in studies evaluating face-to-face CBT (Taylor, 2000).

In conclusion, the results from this study provide evidence to support continued use and development of Internet-based treatment for PD, also in traditional psychiatric care. However, an evaluation comprising a direct comparison with traditional CBT within a regular psychiatric setting should be made. The actual cost-effectiveness of such a treatment should also be evaluated more closely, specifically in relation to traditional psychological treatment.

2.4 STUDY IV. INTERNET- VERSUS GROUP-ADMINISTERED COGNITIVE BEHAVIOUR THERAPY FOR PANIC DISORDER IN A PSYCHIATRIC SETTING: A RANDOMISED TRIAL

2.4.1 Aims

As noted earlier, the distinction between efficacy and effectiveness is regarded as important in treatment outcome research. In this study (Bergström, et al., 2010) the aim was firstly to compare Internet-based CBT with group CBT for patients diagnosed with panic disorder in a regular psychiatric setting. Secondly, our aim was also to evaluate the cost-effectiveness of Internet-based CBT in relation to the more traditional group CBT, which is currently considered to be the most cost-effective psychological treatment commonly used in clinical settings for PD.

2.4.2 Methods

Patients were consecutively referred for participation in the study from either psychiatric out-patient clinics or general practitioners. A third of patients were self-referred to the clinic. After being interviewed by a research nurse in a short telephone screening interview, the patient was assessed in an in-person structured clinical interview conducted by a psychiatrist. The diagnostic part of the clinical interview was based on the M.I.N.I. (Sheehan, et al., 1998).

To be included in the study the patients had to meet the following criteria: 1. Fulfil DSM-IV criteria for PD, 2. Have PD as primary diagnosis, 3. Be above 18 years of age, 4. Not suffer from severe depression or suicidal ideation, 5. If taking prescribed drugs for panic disorder, having had a constant dosage for 2 months prior to commencing treatment in the study, 6. Not undergoing other CBT.

The primary outcome measure was the PDSS (Shear, et al., 1997), described previously (Study III). Other outcomes measures used were the clinician administered Clinical Global Impression Scale (CGI) (Guy, 1976) and MADRS (Montgomery & Åsberg, 1979), as well as the self-report measures Anxiety Sensitivity Index (ASI) (Reiss, Peterson, Gursky, & McNally, 1986) and Sheehan Disability Scale (SDS) (Leon, Olfson, Portera, Farber, & Sheehan, 1997). Information on current work- and/or sick leave-status was obtained in the interview, along with information on duration of PD, history of psychiatric- and/or somatic illness, and current medication. All outcome measures were administered during the clinical interview by a psychiatrist at pre- and post-treatment, as well as after a 6-months follow-up period. The psychiatrists doing the clinical interviews were not informed of treatment status and were thus blind to treatment condition.

The treatment programme consisted of 10 self-help modules which were based on established CBT principles (see Study III). In the Internet treatment the self-help programme was administered via web pages. The group treatment was led by two clinical psychologists and also included the same self-help programme, in the form of printed handouts. In the Internet treatment, access to the next module was given when the clinical psychologist had received the answers to home-work assignments and provided feedback. In the group treatment condition, the groups met with the 2 psychologists during weekly 2-hour sessions. The psychologists involved in the treatment were regular staff psychologists not specially trained for participation in the trial.

The power for the within-group contrasts were estimated based on a conservative effect size of d=0.80, and the sample sizes in each group were regarded as sufficient to detect a within-group effect of this size. Given the previous literature on the effects of CBT for panic disorder we considered a mean standardized difference at or below d= 0.20 as the criteria for equivalence for the main outcome measure PDSS. This is in line with previous psychotherapy research in which d=0.20 is regarded as a minor difference of little clinical importance. We also calculated 95% confidence intervals for the between group effect size. However, we were not able to power the study for the reliable detection of a small between group effect. The obtained power was only robust for a large difference of d=0.50 (two-tailed test, power 75%), which was well above our criteria of equivalence.

The outcome of this trial is not only the between group difference, but also the within-group effects for the two treatments. For these within-group comparisons missing data-points are more critical as effects could be overestimated. A number of patients did not return for the clinical interview at post-treatment or follow-up. A mixed effects models approach was used in the statistical analysis, to adjust for these missing values (Gueorguieva & Krystal, 2004).

Cost-effectiveness ratios were estimated by dividing the treatment cost with the treatment outcome. In addition, incremental cost-effectiveness was determined using a regression framework with costs and effects as dependent variables. All participants who attended at least one Internet- or group session were included in the analysis (n=104).

2.4.3 Results

The between group effect size for the main outcome measure PDSS was d=0.00 (CI95%=-0.41 to 0.41) at post-treatment whereas the between group effect size at 6-month follow-up was d=0.23 (CI95%=-0.15 to 0.62). A majority of patients responded to treatment, when response was defined as a 40% decrease in PDSS scores from pre- to post-treatment and from pre-treatment to follow-up. This was also the case for the CGI and status of PD diagnosis. Dropouts (those patients who refused the post-treatment and/or follow-up interview) were regarded as non-responders.

The mixed effect models clearly show that both treatments had significant impact on all outcome measures over time. However, there were no interactions or differences in estimated means. Hence, both treatments led to statistically significant improvements and were not different according to the mixed effect model accounting for missing data.

The average number of weekly modules completed in the Internet treatment was 6.7 (SD=2.5). The total number of e-mails sent by the therapists during treatment was 555 (mean per patient: 11.3, SD=4.3). The total average therapist time spent per patient in the Internet treatment was 35.4 minutes (SD=19.0). The average number of weekly group sessions attended in the group treatment was 8.1 (SD=2.1). The total average therapist time spent per patient in the group treatment was 6 hours.

The direct cost of the Internet treatment (therapist time and the cost of psychiatrist evaluation) was on average 86 Euros per patient whereas it was 325 Euros for the group treatment. Defining effect as proportion of PDSS responders, the cost-effectiveness analysis showed that Internet treatment had superior cost-effectiveness ratios in relation to group treatment both at post-treatment and follow-up. The direct cost of treatment for each additional PDSS responder was at post-treatment 516 Euros for group treatment and 143 Euros for Internet treatment. At follow up, this cost was 500 Euros and 121 Euros respectively.

2.4.4 Discussion

This study provides evidence for the effectiveness of Internet CBT in a psychiatric setting for referred patients with panic disorder, and suggests that it is not less effective than the more widely used group administered CBT. Both treatments showed large within group effect sizes both at post-treatment and at 6-month follow-up on primary as well as secondary outcome measures. In addition, Internet CBT was more cost-effective than group CBT with respect to direct costs in terms of therapist time.

A majority of patients were considered as responders to treatment, both when this was defined as a significant drop in panic symptoms as well as when defined as degree of global improvement and end-state functioning. Moreover, a majority of patients no longer fulfilled DSM-IV criteria of panic disorder after treatment, and this proportion of patients increased somewhat at the 6-month follow-up.

Given low statistical power for detecting a reliable difference between the two treatments, equivalence between Internet and group CBT for panic disorder cannot be confidently established. However, overall the data suggest that more than half in each group responded to treatment with a substantial decrease in symptoms.

To our knowledge this was the first study comparing Internet administered CBT with group CBT with referred patients in a regular psychiatric setting. The results from this trial provides support for the continued use and dissemination of Internet treatment for panic disorder within psychiatry and suggests that this novel treatment medium has the potential to greatly increase access to evidence based psychological treatments within the health care system.

3 GENERAL DISCUSSION

3.1 MAIN FINDINGS

This thesis provides evidence that Internet-based CBT (self-help guided by brief e-mail contact) is effective in the treatment of symptoms of depression and panic disorder. Internet-based CBT is as effective as traditionally administered group CBT for PD in a regular care setting with patients referred for treatment but considerably more cost-effective.

Study I showed that Internet-based CBT was an effective treatment in reducing symptoms of depression in 85 participants with mild to moderate depression. Compared to a control condition with an online discussion group, the Internet treatment showed large between group effect sizes at post-treatment (Cohen's d=0.94 for the BDI and d=0.79 for the MADRS-S) and improvement was sustained at the 6-month follow-up. Study I can be said to have been replicated by subsequent trials by our group (Holländare, Johnsson, et al., 2010; Vernmark, et al., 2010) as well as independently replicated by an Australian research group in a study reviewed earlier (Perini, et al., 2009). Apart from the fact that no follow-up measurement was made in this Australian trial, its design was virtually identical to the design of Study I. Results were also similar, with a within-group effect size on the BDI of Cohen's d=1.15 (Australian trial) and d=1.22 (Study I), and a between-group effect size on the same measure of d=0.63 (Australian trial) and 0.94 (Study I) respectively. If this latter observation might indicate that Australian trial was somewhat less successful in depressive symptom reduction, this may be due to the fact that it included a more depressed sample.

Study I, being an early trial, preceded many of the studies on Internet treatments for depression reviewed earlier in this thesis. Included in the meta-analysis by Andersson and Cuijpers (2009a), Study I shows larger effect sizes than many of the other non-guided trials therein. Later trials that *have* showed equally large effect sizes have underscored the importance of therapist guidance for effective Internet treatment, or, as in the trial by Spek and co-workers (2007), if not guided, the importance of clear treatment structure and deadline (Andersson, Carlbring, Berger, Almlöv, & Cuijpers, 2009).

Study II analysed predictors of treatment outcome at the 6-month follow-up of Study I. Higher self-reported severity was associated with poorer outcome and a negative correlation was found between number of previous episodes of depression and improvement in treatment. However, the negative correlation between previous number of episodes (M=1.9, SD=1.4) and change score (pre-treatment to follow-up) was weak, and only statistically significant for the BDI change score ($r = -0.26$, $p < .05$) and not for the MADRS-S change score ($r = -0.19$). Demographic variables such as education level and gender showed no relation to treatment outcome. These results are largely in contradiction with a later trial investigating predictors of outcome in Internet CBT for depression (Spek, Nyklicek, et al., 2008) who concluded that the number of previous depressive episodes did not predict poorer outcome, whereas sex of participants and education level did; women and those with higher education profiting more from

treatment. However, as Spek and co-workers points out, their results are rather in contraction with most previous prediction research on traditionally administered CBT (Hamilton & Dobson, 2002; Jarrett, Eaves, Grannemann, & Rush, 1991). The fact that we in Study II did not find a relation between education level and outcome can however be due to a restriction of range effect, since those participating in an Internet treatment may be a more highly educated group as a whole. In sum, with the present evidence, it is difficult to draw firm conclusions about reliable pre-treatment predictors of outcome in Internet treatment. Thus there are relatively few robust predictors of treatment outcome in psychological treatment generally and in guided self-help specifically. The genetic research by our group (Lonsdorf, et al., 2010) however tentatively suggest that this may be a fruitful and yet not well explored research area in which future research could give important information.

Study III showed that Internet-based CBT was effective within a regular psychiatric setting for 20 PD patients referred for treatment. After treatment 75% of patients were considered to have responded to treatment, and at 6-month follow-up this proportion was 70%. Even though being a small trial, it was important as a feasibility study, showing for the first time that Internet treatment was very well integrated within psychiatric care, organisationally as well as technically, and that it was well accepted by staff as well as patients.

Study IV, building upon the experiences from Study III, was a large trial including 104 patients predominantly referred for treatment which showed that Internet-based CBT was equally effective as group-administered CBT within a psychiatric setting. There were no statistically significant differences between the two at post-treatment or at the 6-month follow up. It also evaluated the relative cost-effectiveness of these two treatments, an analysis that showed Internet treatment to be considerably more cost-effective than group treatment with regard to therapist time.

The trials in this thesis have of course several limitations that previously have been discussed separately for each study.

3.2 THERAPIST- AND CLIENT FACTORS AND THE THERAPEUTIC RELATIONSHIP

In the studies in this thesis, the self-help programmes were thus accompanied by obligatory therapist contact. The relative influence of the quality and/or amount of therapist assistance was however not studied.

As reviewed earlier, research suggests that treatment structure (with clear “deadline”) and guidance are probably crucial elements for guided self-help to be effective (Nordin, et al., 2010; Palmqvist, et al., 2007; Spek, Cuijpers, et al., 2007). In trials for both depression and PD evaluating “open” self-help sites with no or poor diagnostic assessment nor defined structure or therapist support, clinical efficacy is more uncertain and the attrition rate us usually very high (Andersson, et al., 2009). In one such trial on

PD (Farvolden, Denisoff, Selby, Bagby, & Rudy, 2005) only 1% (*sic*) of participants completed the proposed self-help modules. As discussed previously, in our Swedish group, special attention has been devoted to these issues (Andersson, Bergström, et al., 2008).

However, it seems that one does not necessarily gain treatment effect by increasing therapist time or involvement over a certain (minimal) threshold. In one study on PD it was shown that increasing therapist contact (from 1 to 3 weekly contacts) did not significantly enhance treatment effect (Klein, et al., 2009). Similar conclusions may be drawn from the study on depression by our group previously discussed (Vernmark, et al., 2010) where a substantial increase in therapist contact did not enhance efficacy. In the studies in this thesis, as well as in most studies of Internet-based guided self-help treatment, the patient's contact with the therapist has consisted of weekly, approximately 10 minute long, interactions. This may very well represent the minimal therapist involvement necessary. However, the threshold or "breaking point" (Palmqvist, et al., 2007) of what constitutes the optimal amount of therapist contact for an effective guided self-help is again not known and future research is warranted here. This threshold is reasonably different between different diagnoses and most probably also depends of the extent of the treatment programme and the amount of interactive supportive functions built into it.

In psychotherapy research, one is of course not only interested in the quantity but also the quality of therapist contact. It is often stated that this therapeutic relationship is central to understanding the effects of therapy (Wampold, 2001). It is however an area of research not extensively developed and where relatively little is yet known about which therapist variables that are particularly important for effective therapy (Beutler, et al., 2003). The influence of individual therapist effects has been specifically studied in Internet-based treatment for depression (Almlöv, Carlbring, Berger, Cuijpers, & Andersson, 2009). The results of the study made the authors suggest that self-help based treatments are probably less sensitive to therapist effects when it comes to those themes directly focused upon in the self-help programme (in this case depressive symptoms) whereas it may play a role when it comes to areas not directly addressed (such as quality of life issues). It is possible that different therapist characteristics, even in Internet treatment, are more or less appropriate for different patient groups (diagnosis) and individuals.

One factor of the individual client that has been proposed to influence outcome of treatment is which preference he or she has for which treatment. In a large study on CBT and pharmacological treatment for (chronic) depression, it was shown that treatment preference was a potent moderator of treatment response for both CBT and pharmacological treatment respectively (Kocsis, et al., 2009). This should be studied more closely within the field of Internet-based treatment.

3.3 NEGATIVE EFFECTS AND POSSIBLE RISKS

Psychotherapy research in general, and maybe CBT research in particular rarely includes structured analyses of negative effects (Barlow, 2010). A possible specific risk with treatments based on self-help that has been evoked (Taylor, 2000) is that they would constitute suboptimal treatments who would leave participants not responding hopeless about the possibility of improvement, and that they thus would not seek subsequent, possibly more effective traditionally administered treatment. There is however no empirical evidence that the risk of negative effects would be greater in guided self-help than in traditional treatment (Scogin, et al., 1996). Nevertheless, these issues should be studied more closely in future research.

3.4 INTERNET TREATMENT AND PSYCHOTHERAPY

One could argue that the development of guided self-help treatments poses interesting questions concerning the very definition of what should be considered to be a "psychological treatment" or "psychotherapy" and how research on them should be pursued. Up until now, no distinction has been made in this thesis between these terms. Renowned CBT researcher David H. Barlow has proposed (2004) that the term psychological treatment should be reserved for evidence-based treatments for discrete medical conditions, whereas psychotherapy would be a broader term including generic therapy not necessarily of discretely diagnosed conditions nor with established efficacy.

So what is then Internet treatment? As Andersson and Cuijpers (2009b) have proposed, it is probably best defined as a psychological treatment. However, Barlow does not necessarily distinguish between guided and non-guided interventions. In my view, pure (un-guided) self-help can best be considered as a prevention programme and thus as a question of public health rather than as a *treatment*. In this view, one of the defining features of a treatment is the fact that the client or patient has been assessed by, and is guided by, a professional who also engages in treatment, by giving at least some feedback or homework etc.

As stressed throughout this thesis, it evaluated *guided* self-help, and with this little word "guided" one thus leaves the area of prevention and pure self-help and one enters the domain of treatment- and psychotherapy research. By doing so one inevitably and fairly quickly encounters several challenges, pertaining to basic issues of what constitutes a "psychological treatment" or "psychotherapy", as evoked by Barlow, but also much more basic and profound issues of theories of science and methodology.

The fact that this thesis evaluated specific, manualised psychological treatments for discretely diagnosed psychiatric disorders by means of quantitative symptom measurement in an experimental design using randomised controlled trials (RCTs), already inscribes it in a medical or experimental tradition that many psychotherapists and researchers have judged inadequate or misleading (Freire, 2006; Sandell, 1987; Wampold, 2001).

Such a research design is closely linked to the definition of what constitutes an empirically supported treatment (EST) and has, during the last 20 years, been increasingly in focus within the field of psychotherapy research (Chambless & Hollon, 1998). This is in part inspired by medical research and evidence-based medicine (Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996). This development has gone hand in hand with evolving managed care policies and the development of clinical practice guidelines. Those who criticise this development either discard it as a whole, claiming that the methods used in EST research (as well as its underlying philosophy of science), like RCTs, are not at all relevant for understanding or studying psychotherapy, or they acknowledge the great merit of these methods, but hold that the exclusive focus on RCTs is not sufficient and leaves many important questions unanswered (Barlow, 1996; Garfield, 1998).

One of the concerns expressed is that, unlike many pharmacological treatments, the mechanisms of action of ESTs are often not well understood and that exclusive focus on RCT-evaluation of broad "treatment packages" abandons important research in understanding psychological mechanisms of action. The Internet treatments evaluated in this thesis are in this sense typical examples of EST research that does not elucidate the mechanisms of action of behaviour- and cognitive therapy outlined in the introduction. There is thus a need for component analyses (Jacobson, et al., 1996) within this area, a type of research design for which Internet treatment could lend itself well, because of the modular structure of most self-help programmes.

Another major concern evoked in psychotherapy research relates to the transferability of highly structured EST protocols into clinical practice, thus highlighting effectiveness (as opposed to efficacy) research (Barlow, 1996; Hunsley & Lee, 2007), an issue that was taken into account in Study III and IV.

It is also worth pointing out that, even if much EST research shares methodological practices with the medical tradition, it may often not share a medical perspective when it comes to the diagnostics or the aetiology of psychiatric disorders (Andersson & Ghaderi, 2006). One example is the view taken by researchers within the behavioural tradition arguing that depression should be "de-medicalised" (Jacobson & Gortner, 2000).

The differences between various forms of psychotherapy apparent in the research literature as for their empirical status as reviewed previously in this thesis can only be understood in the light of the questions raised above. An example is psychoanalytic therapy which, although a highly practised form of psychotherapy in clinical psychiatric settings, is most often scarcely represented in records of ESTs for the most common psychiatric conditions, especially anxiety disorders (Chambless & Ollendick, 2001). Certain researchers within this tradition claim that methods used in EST research are difficult or impossible to apply to psychoanalytically oriented therapies (Leichsenring, 2005). However, other psychotherapy researchers within the psychoanalytic tradition do now argue that such treatments actually can and should be evaluated by methods consistent with EST principles (Busch, Milrod, & Sandberg, 2009).

Internet treatment based on a psychoanalytically informed self-help book (Silverberg, 2005) has in fact been evaluated in one study for generalised anxiety disorder (GAD) (Paxling, et al., 2009). In this still unpublished trial 81 participants with GAD were randomised to Internet-based CBT, Internet-based psychoanalytic treatment, or an untreated control condition. No significant differences were found between the active treatments neither at post-treatment nor at follow-up. However, in this trial the control condition improved significantly as well, leaving the study difficult to interpret.

Another development within research on Internet treatment has been to evaluate the possibility of tailoring treatment to individual client needs, that is to let the treatment content depend more one individual therapist judgement of what is appropriate for the individual client. This has been done not only be evaluating "e-mail therapy" as mentioned previously (Vernmark, et al., 2010) but also by doing "tailored guided self-help" evaluated in two still unpublished studies on Internet CBT for anxiety and depression (Carlbring, et al., 2007; Johansson, 2009). In this approach the therapist chooses, based on client symptomatology, which self-help modules that are to be used as well as their sequence. These studies tentatively suggest that this form of Internet treatment is no less effective but possibly more clinically flexible than the "fixed" Internet CBT treatments used up until now, like those evaluated in this thesis.

Summing up, the field of Internet-based treatment is now, as is the field of psychological treatment as a whole, incorporating more issues and methods traditionally used in psychotherapy research an is thus expanding what up until recently has rather been an exclusive focus on EST research.

3.5 CLINICAL IMPLICATIONS

In the very first National guidelines for the treatment of depression and anxiety disorders recently published by the Swedish National Board of Health and Welfare (2010), the implementation of Internet-based CBT is recommended for the treatment of both depression and PD.

As a consequence of the studies in this thesis, its treatments for depression and PD are now implemented within the Stockholm County Council, making Internet CBT accessible for all potential patients with these diagnoses in the region. This probably makes Stockholm County Council the first public health care service in the world to offer Internet-based psychological treatment to their citizens within regular psychiatric care. Up until now, several hundreds of patients have been treated in this way at the unit of *Internetpsykiatri.se* at Psychiatry Southwest.

It is possible that Internet treatment, precisely by increasing access to empirically supported psychological treatment, may actually change the public perception of what psychotherapy is. Rather than being perceived as something obscure and exclusive, it may become something transparent and accessible. That would be, I think, a good thing.

4 ACKNOWLEDGEMENTS

Doing science is of course, probably even more so than many other human behaviours, a profoundly social enterprise. The worn-out saying "*I could never have done this without you*" can only express a small portion of what I would like to convey to so many people that I have had with me during all these years.

Firstly I would like to express my gratitude to my main supervisor Professor **Nils Lindefors**. He is the one that made this all possible, in a very concrete way, by leading me onto the path of research studies at KI and by inciting me to do "IP1" (Study III) that would turn out to be the pilot project of "KIP" (*Karolinska Internetpsykiatri*), the small seed planted in the fertile soil of the Psychiatry Center Karolinska (PCK) in Solna that was to become the large and prosperous plant of *Internetpsykiatri.se* at Psychiatry Southwest in Huddinge, once Nils had become the main gardener there. He has for me been an infallible support and facilitator. Thank you so much.

I feel just as grateful to my first co-supervisor Professor **Gerhard Andersson.** For being with me from the very start, and for being such a generous and helpful supervisor. Because of his openness, curiosity and breadth of knowledge, Gerhard is in my mind the best scientific role model possible for a psychologist learning to do research. He has been an invaluable inspiration, support and mentor, completely crucial for me being able to arrive to this thesis. *Merci infiniment*.

From the early years in Uppsala there are many more people very important to me who have been with me ever since. A big 'thank you' goes to my second co-supervisor Professor **Per Carlbring** for being so generous with his work and expertise, and for paving the way for Internet CBT research. He is probably, aside his former supervisor Gerhard, one of the most intelligent and most efficient people I know. The best of luck in Umeå!

I can not thank **Fredrik Holländare** enough, for being the first one who actually led me onto this path, for doing "DAVID" (Study I) together with me and for being my very best classmate during five years of psychology studies in Uppsala. Now being beyond the freedom and indignity of Upsalian student life, I miss the beers at Orvars and our discussions on radical behaviourism, politics, and many other things.

This thesis has two parts; depression and panic, Uppsala and Karolinska. Just as I am very indebted to Fredrik for his role in the first part, I am so grateful to **Monica Hellberg** for her role in the second one. Because Monica is Karolinska Institutets very best and most devoted psychiatric research nurse and "IP2" (Study IV) would never have been carried through the way it was if it was not for her.

Many special thanks goes to my colleague **Brjánn Ljótsson** for being so important for Study IV by generously helping me with many aspects of the realisation of this study; everything from doing therapy with me to helping me with data structure and analysis. Many thanks also to **Erik Hedman** and **Erik Andersson** for your much valuable contributions to this study and for being such likeable colleagues.

Of course Fredrik was not the only one involved in Study I. Many thanks to **Lisa Ekselius** and **Viktor Kaldo** for contributing to this trial**,** and to **Daniel Gidlöf** for all the web-application programming he provided in Study I, III and IV.

The Anxiety Disorders Program at PCK was where I not only started the work on the panic trials, but where my career as a clinical psychologist began. I am very grateful to my first clinical supervisor **Andreas Karlsson** for generously and thoughtfully contributing to the panic treatment protocols and for being my first professional role model. I am just as grateful to **Sergej Andréewitch** and **Christian Rück**, who created the Anxiety Disorders Program, for making many crucial contributions to the panic trials, among other things by doing the psychiatric assessments on a huge amount of patients. With Andreas, Sergej and Christian I have not only shared several years of everyday clinical work but also some not so everyday conference trips. Snow storms in Toronto and late night drinks in Miami Beach wouldn't have been the same without these really nice guys.

I have had the chance to, from the start, be able to combine work as a clinical psychologist with research studies and this great opportunity that I have had leaves me grateful to many important people. First among them is of course Nils, not only my main supervisor but also the Head of Psychiatry Southwest. **Peter Nordström**, former Head of PCK, was the one who coined the term "*Internetpsykiatri*" and who much created the fertile soil of research possibilities I mentioned earlier at PCK. Head of Psychiatry Northwest **Maj-Britt Larsson Gladh** and **Sven Nordlund** welcomed me back to Solna for clinical work and supported my research. On the academic side, my gratitude to the Center for Psychiatry Research and its Head **Johan Franck** for research leave opportunities and for letting me take part in the Research school for clinicians in psychiatry. I am also grateful to my department, the Department of Clinical Neuroscience, and Professor **Martin Ingvar**, Director of Research Education **Bob Harris**, as well as Study administrator **Marianne Youssefi**. And thank you **Tina Lonsdorf, Arne Öhman** and **Martin Schalling** for good spirited scientific co-operation in doing the interesting genetic work with data from Study IV.

I gratefully acknowledge that the studies in this thesis were funded by the Stockholm County Council, the Swedish Research Council and the L.J. Boethius Foundation.

There are many people at PCK to whom I would like to convey my gratitude. **Håkan Nyman**, **Gabriella Oxenstierna** and fellow *francophile* **Jussi Jokinen** for hiring me in the first place. **Diana Radu-Djurfeldt** for contributing to psychiatric assessment in the panic trials, and for being such a likeably colleague and fellow researcher. **Marita Signarsson** for much help and administrative aid, not least in organising my half-time seminar and my dissertation. And then of course my fellow clinical colleagues through the years with whom I've shared many good-humoured coffee breaks, and from whom I've received much cheerful support and sarcasms. Thank you **Per Lundström, Annelie Holmström**, **Yvonne Sedlenieks**, **Lena Lindberg**, **Peter Csatlós**, **Hanna-Sahlin-Berg**, **Maria Wiklander**, **Linda Lövefors**, **Matilda Larsson, Maria Nordell** and **Pontus Bjurner**.

After a very helpful *congé personnel* in Paris I reconnected with my doctoral project by coming to Psychiatry Southwest in Huddinge and participating in the very interesting start-up year of *Internetpsykiatri.se*. I am actually very proud to see that the results of this thesis and the programmes for depression and panic finally entered into clinical practice, which probably is a worlds-first within regular psychiatric care. What better outcome of his efforts could a clinical researcher ask for? Thank you Christian, Brjánn, Erik, Erik and Viktor as well as **Liselotte Jansson**, **Anne-Christine Fredman** and **Anna-Clara Hellstadius** for every-day support, humour and the long buffet-lunches at MF.

For me doing psychotherapy research has been naturally linked to doing therapy. The last three years of my life as a PhD-student were also those of having the chance to become a licensed psychotherapist at the Psychology department of Stockholm University. Thank you **Lars-Göran Öst** for always having been the giant of Swedish behaviour therapy and for letting so many of us youngsters stand on your shoulders. I am also very grateful to **Jonas Ramnerö** for being such an inspiring teacher and scientist-practitioner role model and to **Elisabeth Breitholtz** for making me a better therapist.

Another for me important person in my development as a therapist is **Sandra Bates**. Sandra has, ever since my first trembling steps with my very first therapy client 10 years ago, been my senior clinical supervisor and thus has nurtured me with her tremendous experience, to-the-point stance, and great sense of humour. My gratitude goes also to my friend **Herman de Vries,** not only for proofreading this thesis, but also for the many interesting talks we have had on *l'analyse fonctionnelle,* clinical cases and many other topics during countryside walks with the dogs at Louveaucourt and *des petit-déjs au Cépage Montmartrois*.

I certainly have many dear friends who mean a lot to me. Thanks for being there **Robert**, **Marthin**, **Per**, **Johan & Jakob**, **Johan & Emma, Henrik, Karl, Sofia, Hans, Johan, Elin, Rebecca, Ulrika, Nathan** and **Stéphanie**.

Ulla and **Mats,** mom and dad; thank you for having given me so much love, and for always having supported me, in big and in small. The best I have, I got from you. Finishing this thesis, I can not help but hear a familiar voice in my head saying: "*Det vill gärna bli bra!"*. I agree, dad. And, thank you **Lennart** for being who you are. A big hug goes to my dear big brother **Hans**. Talking of role models – when growing up, you were always my greatest one. I'm so thankful that I have you in my life, as well as **Linda**, **Ebba** and **Oskar**. You're my family.

*Et en guise de fin - puisqu'il faut quand même mettre une cerise sur ce gâteau - de grosses bises à ma chère âme sœur **Marie** avec laquelle j'ai pu sentir, plus profondément qu'avant, au rez-de-jardin de la Bibliothèque Nationale de France à Paris, la vraie joie de la vie doctorante et de la recherche. Merci.*

5 REFERENCES

Aggen, S. H., Neale, M. C., & Kendler, K. S. (2005). DSM criteria for major depression: evaluating symptom patterns using latent-trait item response models. *Psychological Medicine, 35*(4), 475-487.

Agras, S., Leitenberg, H., & Barlow, D. H. (1968). Social reinforcement in the modification of agoraphobia. *Archives of general psychiatry, 19*(4), 423-427.

Albert, U., Maina, G., Bergesio, C., & Bogetto, F. (2006). Axis I and II comorbidities in subjects with and without nocturnal panic. *Depression and anxiety, 23*(7), 422-428.

Almlöv, J., Carlbring, P., Berger, T., Cuijpers, P., & Andersson, G. (2009). Therapist factors in internet-delivered cognitive behavioural therapy for major depressive disorder. *Cognitive Behaviour Therapy, 38*(4), 247-254.

Alston, E. F. (1962). Bibliotherapy and psychotherapy. *Library Trends, 11*, 159-176.

American Psychiatric Association (1987). *Diagnostic and statistical manual of mental disorders - 3rd edition revised (DSM-III-R)*. Washington DC: American Psychiatric Press.

American Psychiatric Association (1998). Practice guideline for the treatment of patients with panic disorder. Work Group on Panic Disorder. *The American Journal of Psychiatry, 155*(5 Suppl), 1-34.

American Psychiatric Association (2000a). *Diagnostic and Statistical Manual of Mental Disorders - 4th edition (DSM-IV)* (4th edition, text revision edition ed.). Washington DC: American Psychiatric Press.

American Psychiatric Association (2000b). Practice guideline for the treatment of patients with major depressive disorder (revision). *The American Journal of Psychiatry, 157*(4 suppl), 1-45.

American Psychiatric Association (2010a). Agoraphobia - proposed revision. *DSM-5 Development (www.dsm5.org)* Retrieved 15 march 2010

American Psychiatric Association (2010b). Mixed Anxiety Depression - proposed revision. *DSM-5 Development (www.dsm5.org)* Retrieved 15 march 2010

American Psychiatric Association (2010c). Panic disorder - proposed revision. *DSM-5 Development (www.dsm5.org)* Retrieved 15 march 2010

Anderson, L., Lewis, G., Araya, R., Elgie, R., Harrison, G., Proudfoot, J., Schmidt, U., Sharp, D., Weightman, A., & Williams, C. (2005). Self-help books for depression: how can practitioners and patients make the right choice? *The British journal of general practice, 55*(514), 387-392.

Andersson, G. (2009). Using the Internet to provide cognitive behaviour therapy. *Behaviour Research and Therapy, 47*(3), 175-180.

Andersson, G., Bergström, J., Buhrman, M., Carlbring, P., Holländare, F., Kaldo, V., Nilsson-Ihrfelt, E., Paxling, B., Ström, L., & Waara, J. (2008). Development of a New Approach to Guided Self-Help via the Internet: The Swedish Experience. *Journal of Technology in Human Services, 26*(2), 161 - 181.

Andersson, G., Bergström, J., Carlbring, P., & Lindefors, N. (2005). The use of the Internet in the treatment of anxiety disorders. *Current opinion in psychiatry, 18*(1), 73-77.

Andersson, G., Bergström, J., Holländare, F., Carlbring, P., Kaldo, V., & Ekselius, L. (2005). Internet-based self-help for depression: randomised controlled trial. *The British Journal of Psychiatry, 187*(5), 456-461.

Andersson, G., Bergström, J., Holländare, F., Ekselius, L., & Carlbring, P. (2004). Delivering CBT for depression via the Internet. Predicting outcome at 6-months follow-up. *Verhaltenstherapie, 14*(3), 185-189.

Andersson, G., Bergström, J., Holländare, F., Lenndin, J., & Vernmark, K. (2007). *Ut ur depression och nedstämdhet med kognitiv beteendeterapi : ett effektivt självhjälpsprogram*. Stockholm: Viva.

Andersson, G., & Carlbring, P. (2003). Internet and cognitive behaviour therapy: new opportunities for treatment and assessment. *Cognitive Behaviour Therapy, 32*(3), 97-99.

Andersson, G., Carlbring, P., Berger, T., Almlöv, J., & Cuijpers, P. (2009). What Makes Internet Therapy Work? *Cognitive Behaviour Therapy, 38*(1 supp 1), 55 - 60.

Andersson, G., Carlbring, P., & Grimlund, A. (2008). Predicting treatment outcome in internet versus face to face treatment of panic disorder. *Computers in Human Behavior, 24*(5), 1790-1801.

Andersson, G., & Cuijpers, P. (2009a). Internet-based and other computerized psychological treatments for adult depression: a meta-analysis. *Cognitive Behaviour Therapy, 38*(4), 196-205.

Andersson, G., & Cuijpers, P. (2009b). 'Psychological treatment' as an umbrella term for evidence-based psychotherapies? *Nordic Psychology, 61*(2), 4-15.

Andersson, G., & Ghaderi, A. (2006). An overview and analysis of the behaviorist criticism of the diagnostic and statistical manual of mental disorders (DSM). *Clinical Psychologist, 10*, 67–77.

Andrade, L., Caraveo-Anduaga, J. J., Berglund, P., Bijl, R. V., De Graaf, R., Vollebergh, W., Dragomirecka, E., Kohn, R., Keller, M., Kessler, R. C., Kawakami, N., Kilic, C., Offord, D., Ustun, T. B., & Wittchen, H. U. (2003). The epidemiology of major depressive episodes: results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. *International journal of methods in psychiatric research, 12*(1), 3-21.

Arroll, B., Elley, C. R., Fishman, T., Goodyear-Smith, F. A., Kenealy, T., Blashki, G., Kerse, N., & Macgillivray, S. (2009). Antidepressants versus placebo for depression in primary care. *The Cochrane database of systematic reviews*(3), CD007954.

Artigas, F., Nutt, D. J., & Shelton, R. (2002). Mechanism of action of antidepressants. *Psychopharmacology Bulletin, 36 Suppl 2*, 123-132.

Ashton, H. (2005). The diagnosis and management of benzodiazepine dependence. *Current opinion in psychiatry, 18*(3), 249-255.

Austin, J., & Carr, J. E. (2000). *Handbook of Applied Behavior Analysis*. Reno: Context Press.

Baer, L., Greist, J., & Marks, I. M. (2007). Computer-aided cognitive behaviour therapy. *Psychotherapy and Psychosomatics, 76*(4), 193-195.

Bakker, A., van Balkom, A. J., & Spinhoven, P. (2002). SSRIs vs. TCAs in the treatment of panic disorder: a meta-analysis. *Acta Psychiatrica Scandinavica, 106*(3), 163-167.

Ballenger, J. C., Burrows, G. D., DuPont, R. L., Jr., Lesser, I. M., Noyes, R., Jr., Pecknold, J. C., Rifkin, A., & Swinson, R. P. (1988). Alprazolam in panic disorder and agoraphobia: results from a multicenter trial. I. Efficacy in short-term treatment. *Archives of general psychiatry, 45*(5), 413-422.

Barlow, D. H. (1996). Health care policy, psychotherapy research, and the future of psychotherapy. *American psychologist, 51*(10), 1050-1058.

Barlow, D. H. (2002). *Anxiety and Its Disorders: The Nature and Treatment of Anxiety and Panic* (2nd ed.). New York: Guilford Press.

Barlow, D. H. (2004). Psychological treatments. *American psychologist, 59*(9), 869-878.

Barlow, D. H. (2010). Negative effects from psychological treatments: a perspective. *American psychologist, 65*(1), 13-20.

Barlow, D. H., Cohen, A. S., Waddell, M. T., Vermilyea, B. B., Klosko, J. S., Blanchard, E. B., & Di Nardo, P. A. (1984). Panic and generalized anxiety disorders: Nature and treatment. *Behavior Therapy, 15*(5), 431-449.

Barlow, D. H., & Craske, M. G. (2000). *Mastery of your anxiety and panic (MAP-3)*. San Antonio: The Psychological Corporation.

Barlow, D. H., Gorman, J. M., Shear, M. K., & Woods, S. W. (2000). Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: A randomized controlled trial. *Journal of the American Medical Association, 283*(19), 2529-2536.

Batelaan, N. M., de Graaf, R., Spijker, J., Smit, J. H., van Balkom, A. J., Vollebergh, W. A., & Beekman, A. T. (2010). The course of panic attacks in individuals with panic disorder and subthreshold panic disorder: a population-based study. *Journal of Affective Disorders, 121*(1-2), 30-38.

Beck, A. T., Emery, G., & Greenberg, R. (1985). *Anxiety Disorders and Phobias: A Cognitive Perspective*. New York: Basic Books.

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology, 56*(6), 893-897.

Beck, A. T., Rush, A. J., Shaw, B. F., & Emery, G. (1979). *Cognitive Therapy of Depression*. New York: Guilford Press.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An Inventory for Measuring Depression. *Archives of general psychiatry, 4*(6), 561-571.

Beck, J. S. (1995). *Cognitive Therapy: Basics and Beyond*. New York: Guilford Press.

Bell, C. J., & Nutt, D. J. (1998). Serotonin and panic. *The British Journal of Psychiatry, 172*, 465-471.

Benedikt, M. (1870). Über Platzschwindel. *Allgemeine Wiener Medizinische Zeitung, 15*, 488-490.

Bergström, J., Andersson, G., Karlsson, A., Andréewitch, S., Rück, C., Carlbring, P., & Lindefors, N. (2009). An open study of the effectiveness of Internet treatment for panic disorder delivered in a psychiatric setting. *Nordic journal of psychiatry, 63*(1), 44-50.

Bergström, J., Andersson, G., Ljótsson, B., Rück, C., Andréewitch, S., Karlsson, A., Carlbring, P., Andersson, E., & Lindefors, N. (2010). *Internet- versus Group-administered Cognitive Behaviour Therapy for Panic Disorder in a Psychiatric Setting: A Randomised Trial*.Unpublished manuscript.

Beutler, L. E., Malik, M., Alimohamed, S., Harwood, T. M., Talebi, H., Noble, S., & Wong, E. (2003). Therapist variables. In Lambert, M. J. (Ed.), *Bergin and Garfield's handbook of psychotherapy and behavior change* (pp. 227-326). New York: Wiley.

Bienvenu, O. J., Onyike, C. U., Stein, M. B., Chen, L. S., Samuels, J., Nestadt, G., & Eaton, W. W. (2006). Agoraphobia in adults: incidence and longitudinal relationship with panic. *The British Journal of Psychiatry, 188*, 432-438.

Bienvenu, O. J., Stein, M. B., Samuels, J. F., Onyike, C. U., Eaton, W. W., & Nestadt, G. (2009). Personality disorder traits as predictors of subsequent first-onset panic disorder or agoraphobia. *Comprehensive Psychiatry, 50*(3), 209-214.

Blaya, C., Salum, G. A., Lima, M. S., Leistner-Segal, S., & Manfro, G. G. (2007). Lack of association between the Serotonin Transporter Promoter Polymorphism (5-HTTLPR) and Panic Disorder: a systematic review and meta-analysis. *Behavioral and brain functions, 3*, 41.

Blazer, D. G. (2005). Depression and social support in late life: a clear but not obvious relationship. *Aging & mental health, 9*(6), 497-499.

Boschen, M. J. (2008). Publication trends in individual anxiety disorders: 1980-2015. *Journal of Anxiety Disorders, 22*(3), 570-575.

Bowman, D., Scogin, F., & Lyrene, B. (1995). The Efficacy of Self-Examination Therapy and Cognitive Bibliotherapy in the Treatment of Mild to Moderate Depression. *Psychotherapy Research, 5*(2), 131 - 140.

Broome, J. (1993). QALYs. *Journal of Public Economics, 50*(2), 149-167.

Bruce, S. E., Vasile, R. G., Goisman, R. M., Salzman, C., Spencer, M., Machan, J. T., & Keller, M. B. (2003). Are benzodiazepines still the medication of choice for patients with panic disorder with or without agoraphobia? *The American Journal of Psychiatry, 160*(8), 1432-1438.

Bruce, S. E., Yonkers, K. A., Otto, M. W., Eisen, J. L., Weisberg, R. B., Pagano, M., Shea, M. T., & Keller, M. B. (2005). Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. *The American Journal of Psychiatry, 162*(6), 1179-1187.

Burns, D. D. (1999). *Feeling Good. The New Mood Therapy*. New York: Avon Books.

Busch, F. N., Milrod, B. L., & Sandberg, L. S. (2009). A study demonstrating efficacy of a psychoanalytic psychotherapy for panic disorder: implications for psychoanalytic research, theory, and practice. *Journal of the American Psychoanalytic Association, 57*(1), 131-148.

Campo-Soria, C., Chang, Y., & Weiss, D. S. (2006). Mechanism of action of benzodiazepines on GABA(a) receptors. *British Journal of Pharmacology, 148*(7), 984-990.

Carlbring, P., Bohman, S., Brunt, S., Buhrman, M., Westling, B. E., Ekselius, L., & Andersson, G. (2006). Remote treatment of panic disorder: a randomized trial of internet-based cognitive behavior therapy supplemented with telephone calls. *The American Journal of Psychiatry, 163*(12), 2119-2125.

Carlbring, P., Ekselius, L., & Andersson, G. (2003). Treatment of panic disorder via the Internet: a randomized trial of CBT vs. applied relaxation. *Journal of Behavior Therapy and Experimental Psychiatry, 34*(2), 129-140.

Carlbring, P., Gustafsson, H., Ekselius, L., & Andersson, G. (2002). 12-month prevalence of panic disorder with or without agoraphobia in the Swedish general population. *Social Psychiatry and Psychiatric Epidemiology, 37*(5), 207-211.

Carlbring, P., Maurin, L., Törngren, L., Linna, E., Sparthan, E., & Andersson, G. (2007). *NOVA: Individualized Internet- delivered guided self-help for anxiety*

disorders: A randomized controlled study. Paper presented at the Third meeting of the International Society for Research on Internet Interventions.

Carlbring, P., Nilsson-Ihrfelt, E., Waara, J., Kollenstam, C., Buhrman, M., Kaldo, V., Soderberg, M., Ekselius, L., & Andersson, G. (2005). Treatment of panic disorder: live therapy vs. self-help via the Internet. *Behaviour Research and Therapy, 43*(10), 1321-1333.

Carlbring, P., Westling, B. E., & Andersson, G. (2000). A Review of Published Self-help Books for Panic Disorder. *Cognitive Behaviour Therapy, 29*(1), 5 - 13.

Carlbring, P., Westling, B. E., Ljungstrand, P., Ekselius, L., & Andersson, G. (2001). Treatment of panic disorder via the internet: A randomized trial of a self-help program. *Behavior Therapy, 32*(4), 751-764.

Carr, A. C., & Ghosh, A. (1983). Response of phobic patients to direct computer assessment. *The British Journal of Psychiatry, 142*, 60-65.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., & Poulton, R. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science, 301*(5631), 386-389.

Chambless, D. L., Caputo, G. C., Jasin, S. E., Gracely, E. J., & Williams, C. (1985). The Mobility Inventory for Agoraphobia. *Behaviour Research and Therapy, 23*(1), 35-44.

Chambless, D. L., & Hollon, S. D. (1998). Defining empirically supported therapies. *Journal of Consulting and Clinical Psychology, 66*(1), 7-18.

Chambless, D. L., & Ollendick, T. H. (2001). Empirically supported psychological interventions: controversies and evidence. *Annual Review of Psychology, 52*, 685-716.

Chouinard, G. (2004). Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. *The journal of clinical psychiatry, 65 Suppl 5*, 7-12.

Christensen, H., Griffiths, K. M., & Jorm, A. F. (2004). Delivering interventions for depression by using the internet: randomised controlled trial. *British Medical Journal, 328*(7434), 265.

Christensen, H., Griffiths, K. M., Mackinnon, A. J., & Brittliffe, K. (2006). Online randomized controlled trial of brief and full cognitive behaviour therapy for depression. *Psychological Medicine, 36*(12), 1737-1746.

Cipriani, A., Furukawa, T. A., Salanti, G., Geddes, J. R., Higgins, J. P., Churchill, R., Watanabe, N., Nakagawa, A., Omori, I. M., McGuire, H., Tansella, M., & Barbui, C. (2009). Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet, 373*(9665), 746-758.

Clark, D. M. (1986). A cognitive approach to panic. *Behaviour Research and Therapy, 24*(4), 461-470.

Clark, D. M., Layard, R., Smithies, R., Richards, D. A., Suckling, R., & Wright, B. (2009). Improving access to psychological therapy: Initial evaluation of two UK demonstration sites. *Behaviour Research and Therapy*.

Clarke, G., Eubanks, D., Reid, E., Kelleher, C., O'Connor, E., DeBar, L. L., Lynch, F., Nunley, S., & Gullion, C. (2005). Overcoming Depression on the Internet (ODIN) (2): a randomized trial of a self-help depression skills program with reminders. *Journal of medical Internet research, 7*(2), e16.

Clarke, G., Kelleher, C., Hornbrook, M., Debar, L., Dickerson, J., & Gullion, C. (2009). Randomized effectiveness trial of an internet, pure self-help, cognitive

behavioral intervention for depressive symptoms in young adults. *Cognitive Behaviour Therapy, 38*(4), 222-234.

Clarke, G., Reid, E., Eubanks, D., O'Connor, E., DeBar, L. L., Kelleher, C., Lynch, F., & Nunley, S. (2002). Overcoming depression on the Internet (ODIN): a randomized controlled trial of an Internet depression skills intervention program. *Journal of medical Internet research, 4*(3), E14.

Clayton, A. H., Stewart, R. S., Fayyad, R., & Clary, C. M. (2006). Sex differences in clinical presentation and response in panic disorder: pooled data from sertraline treatment studies. *Archives of Women's Mental Health, 9*(3), 151-157.

Clum, G. A., & Surls, R. (1993). A meta-analysis of treatments for panic disorder. *Journal of Consulting and Clinical Psychology, 61*(2), 317-326.

Craske, M. G., Lang, A. J., Mystkowski, J. L., Zucker, B. G., Bystritsky, A., & Yan-Go, F. (2002). Does nocturnal panic represent a more severe form of panic disorder? *Journal of nervous and mental disease, 190*(9), 611-618.

Cuijpers, P. (1997). Bibliotherapy in unipolar depression: a meta-analysis. *Journal of Behavior Therapy and Experimental Psychiatry, 28*(2), 139-147.

Cuijpers, P. (1998). A psychoeducational approach to the treatment of depression: A meta-analysis of lewinsohn's "coping with depression" course. *Behavior Therapy, 29*(3), 521-533.

Cuijpers, P., van Straten, A., Andersson, G., & van Oppen, P. (2008). Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. *Journal of Consulting and Clinical Psychology, 76*(6), 909-922.

Cuijpers, P., van Straten, A., Bohlmeijer, E., Hollon, S. D., & Andersson, G. (2009). The effects of psychotherapy for adult depression are overestimated: a meta-analysis of study quality and effect size. *Psychological Medicine*, 1-13.

Cuijpers, P., van Straten, A., & Warmerdam, L. (2007). Behavioral activation treatments of depression: a meta-analysis. *Clinical Psychology Review, 27*(3), 318-326.

Cuijpers, P., van Straten, A., Warmerdam, L., & Andersson, G. (2009). Psychotherapy versus the combination of psychotherapy and pharmacotherapy in the treatment of depression: a meta-analysis. *Depression and anxiety, 26*(3), 279-288.

Dannon, P. N., Iancu, I., Lowengrub, K., Gonopolsky, Y., Musin, E., Grunhaus, L., & Kotler, M. (2007). A naturalistic long-term comparison study of selective serotonin reuptake inhibitors in the treatment of panic disorder. *Clinical neuropharmacology, 30*(6), 326-334.

de Graaf, L. E., Gerhards, S. A. H., Arntz, A., Riper, H., Metsemakers, J. F. M., Evers, S. M. A. A., Severens, J. L., Widdershoven, G., & Huibers, M. J. H. (2009). Clinical effectiveness of online computerised cognitive-behavioural therapy without support for depression in primary care: randomised trial. *The British Journal of Psychiatry, 195*(1), 73-80.

de las Cuevas, C., Sanz, E., & de la Fuente, J. (2003). Benzodiazepines: more "behavioural" addiction than dependence. *Psychopharmacology (Berl), 167*(3), 297-303.

den Boer, P. C., Wiersma, D., & Van den Bosch, R. J. (2004). Why is self-help neglected in the treatment of emotional disorders? A meta-analysis. *Psychological Medicine, 34*(6), 959-971.

DeRubeis, R. J., Gelfand, L. A., Tang, T. Z., & Simons, A. D. (1999). Medications versus cognitive behavior therapy for severely depressed outpatients: mega-

analysis of four randomized comparisons. *The American Journal of Psychiatry, 156*(7), 1007-1013.

DeRubeis, R. J., Hollon, S. D., Amsterdam, J. D., Shelton, R. C., Young, P. R., Salomon, R. M., O'Reardon, J. P., Lovett, M. L., Gladis, M. M., Brown, L. L., & Gallop, R. (2005). Cognitive therapy vs medications in the treatment of moderate to severe depression. *Archives of general psychiatry, 62*(4), 409-416.

Deutsch, S. I., Rosse, R. B., Sud, I. M., & Burket, J. A. (2009). Temporal lobe epilepsy confused with panic disorder: implications for treatment. *Clinical neuropharmacology, 32*(3), 160-162.

Dimidjian, S., Hollon, S. D., Dobson, K. S., Schmaling, K. B., Kohlenberg, R. J., Addis, M. E., Gallop, R., McGlinchey, J. B., Markley, D. K., Gollan, J. K., Atkins, D. C., Dunner, D. L., & Jacobson, N. S. (2006). Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. *Journal of Consulting and Clinical Psychology, 74*(4), 658-670.

Dobson, K. S. (1989). A meta-analysis of the efficacy of cognitive therapy for depression. *Journal of Consulting and Clinical Psychology, 57*(3), 414-419.

Dobson, K. S., Hollon, S. D., Dimidjian, S., Schmaling, K. B., Kohlenberg, R. J., Gallop, R. J., Rizvi, S. L., Gollan, J. K., Dunner, D. L., & Jacobson, N. S. (2008). Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the prevention of relapse and recurrence in major depression. *Journal of Consulting and Clinical Psychology, 76*(3), 468-477.

Drummond, M. F., Sculpher, M. J., Torrance, G. W., O'Brien, B. J., & Stoddart, G. L. (2005). *Methods for the economic evaluation of health care programmes.* Oxford: Oxford University Press.

Duman, R. S., Malberg, J., & Thome, J. (1999). Neural plasticity to stress and antidepressant treatment. *Biological psychiatry, 46*(9), 1181-1191.

Dunlop, B. W., & Davis, P. G. (2008). Combination Treatment With Benzodiazepines and SSRIs for Comorbid Anxiety and Depression: A Review. *Primary care companion to the Journal of clinical psychiatry, 10*(3), 222-228.

Eaton, W. W., Anthony, J. C., Romanoski, A., Tien, A., Gallo, J., Cai, G., Neufeld, K., Schlaepfer, T., Laugharne, J., & Chen, L. S. (1998). Onset and recovery from panic disorder in the Baltimore Epidemiologic Catchment Area follow-up. *The British Journal of Psychiatry, 173*, 501-507.

Eaton, W. W., Kessler, R. C., Wittchen, H. U., & Magee, W. J. (1994). Panic and panic disorder in the United States. *The American Journal of Psychiatry, 151*(3), 413-420.

Elkin, I., Shea, M. T., Watkins, J. T., Imber, S. D., Sotsky, S. M., Collins, J. F., Glass, D. R., Pilkonis, P. A., Leber, W. R., Docherty, J. P., & et al. (1989). National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments. *Archives of general psychiatry, 46*(11), 971-982; discussion 983.

Eysenck, H. J. (1960). *Behavior Therapy and the Neuroses.* New York: Pergamon Press.

Farvolden, P., Denisoff, E., Selby, P., Bagby, R. M., & Rudy, L. (2005). Usage and longitudinal effectiveness of a Web-based self-help cognitive behavioral therapy program for panic disorder. *Journal of medical Internet research, 7*(1), e7.

Fava, M., Hwang, I., Rush, A. J., Sampson, N., Walters, E. E., & Kessler, R. C. (2009). The importance of irritability as a symptom of major depressive disorder: results from the National Comorbidity Survey Replication. *Molecular Psychiatry*.

Ferster, C. B. (1973). A functional anlysis of depression. *American psychologist, 28*(10), 857-870.

First, M. B., Gibbon, M., Spitzer, R. L., & Williams, J. B. W. (1996). *Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I)*. New York: New York Psychiatric Institute.

Freire, E. S. (2006). Randomized Controlled Clinical Trial in Psychotherapy Research: An Epistemological Controversy. *Journal of Humanistic Psychology, 46*(3), 323-335.

Frisch, M. B., Cornell, J., Villanueva, M., & Retzlaff, P. J. (1992). Clinical Validation of the Quality of Life Inventory: A Measure of Life Satisfaction for Use in Treatment Planning and Outcome Assessment. *Psychological Assessment, 4*(1), 92-10.

Furukawa, T. A., Watanabe, N., & Churchill, R. (2006). Psychotherapy plus antidepressant for panic disorder with or without agoraphobia: systematic review. *The British Journal of Psychiatry, 188*, 305-312.

Garfield, S. L. (1998). Some comments on empirically supported treatments. *Journal of Consulting and Clinical Psychology, 66*(1), 121-125.

Garland, A. F., Hurlburt, M. S., Brookman-Frazee, L., Taylor, R. M., & Accurso, E. C. (2009). Methodological Challenges of Characterizing Usual Care Psychotherapeutic Practice. *Administration and Policy in Mental Health and Mental Health Services Research.*

Geddes, J. R., Carney, S. M., Davies, C., Furukawa, T. A., Kupfer, D. J., Frank, E., & Goodwin, G. M. (2003). Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet, 361*(9358), 653-661.

Gelder, M. G., & Marks, I. M. (1966). Severe agoraphobia: a controlled prospective trial of behaviour therapy. *The British Journal of Psychiatry, 112*(484), 309-319.

Gellatly, J., Bower, P., Hennessy, S., Richards, D., Gilbody, S., & Lovell, K. (2007). What makes self-help interventions effective in the management of depressive symptoms? Meta-analysis and meta-regression. *Psychological Medicine, 37*(9), 1217-1228.

Ghosh, A., Marks, I. M., & Carr, A. C. (1984). Controlled study of self-exposure treatment for phobics: preliminary communication. *Journal of the Royal Society of Medicine, 77*(6), 483-487.

Ghosh, A., Marks, I. M., & Carr, A. C. (1988). Therapist contact and outcome of self-exposure treatment for phobias. A controlled study. *The British Journal of Psychiatry, 152*, 234-238.

Glasgow, R. E., & Rosen, G. M. (1978). Behavioral bibliotherapy: a review of self-help behavior therapy manuals. *Psychological bulletin, 85*(1), 1-23.

Gloaguen, V., Cottraux, J., Cucherat, M., & Blackburn, I. M. (1998). A meta-analysis of the effects of cognitive therapy in depressed patients. *Journal of Affective Disorders, 49*(1), 59-72.

Goldiamond, I. (1976). Singling out self-administered behavior therapies for professional overview. A comment on Rosen. *American psychologist, 31*(2), 142-147.

Goodwin, R. D. (2003). The prevalence of panic attacks in the United States: 1980 to 1995. *Journal of clinical epidemiology, 56*(9), 914-916.

Goodwin, R. D., Faravelli, C., Rosi, S., Cosci, F., Truglia, E., de Graaf, R., & Wittchen, H. U. (2005). The epidemiology of panic disorder and agoraphobia in Europe. *European Neuropsychopharmacology, 15*(4), 435-443.

Gortner, E. T., Gollan, J. K., Dobson, K. S., & Jacobson, N. S. (1998). Cognitive-behavioral treatment for depression: relapse prevention. *Journal of Consulting and Clinical Psychology, 66*(2), 377-384.

Gould, R. A., & Clum, G. A. (1993). A meta-analysis of self-help treatment approaches. *Clinical Psychology Review, 13*(2), 169-186.

Gould, R. A., Clum, G. A., & Shapiro, D. (1993). The use of bibliotherapy in the treatment of panic: A preliminary investigation. *Behavior Therapy, 24*(2), 241-252.

Grant, B. F., Hasin, D. S., Stinson, F. S., Dawson, D. A., Goldstein, R. B., Smith, S., Huang, B., & Saha, T. D. (2006). The epidemiology of DSM-IV panic disorder and agoraphobia in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *The journal of clinical psychiatry, 67*(3), 363-374.

Gregory, R. J., Canning, S. S., Lee, T. W., & Wise, J. C. (2004). Cognitive Bibliotherapy for Depression: A Meta-Analysis. *Professional Psychology - Research & Practice, 35*(3), 275-280.

Gueorguieva, R., & Krystal, J. H. (2004). Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. *Archives of general psychiatry, 61*(3), 310-317.

Guy, W. (1976). Clinical Global Impressions *ECDEU Manual, US Dept of Health and Human Services* (pp. 217-222). Rockville, MD: NIMH.

Hamilton, K. E., & Dobson, K. S. (2002). Cognitive therapy of depression: pretreatment patient predictors of outcome. *Clinical Psychology Review, 22*(6), 875-893.

Hettema, J. M., Neale, M. C., & Kendler, K. S. (2001). A review and meta-analysis of the genetic epidemiology of anxiety disorders. *The American Journal of Psychiatry, 158*(10), 1568-1578.

Hirshbein, L. D. (2006). Science, gender, and the emergence of depression in American psychiatry, 1952-1980. *Journal of the History of Medicine and Allied Sciences, 61*(2), 187-216.

Hoagwood, K., Hibbs, E., Brent, D., & Jensen, P. (1995). Introduction to the special section: efficacy and effectiveness in studies of child and adolescent psychotherapy. *Journal of Consulting and Clinical Psychology, 63*(5), 683-687.

Hohl, E., Berger, T., Bergström, J., Andersson, G., & Caspar, F. (2010). *Traitements psychologiques basés sur Internet : caractéristiques et évidences empiriques*.Unpublished manuscript.

Hollon, S. D., DeRubeis, R. J., Shelton, R. C., Amsterdam, J. D., Salomon, R. M., O'Reardon, J. P., Lovett, M. L., Young, P. R., Haman, K. L., Freeman, B. B., & Gallop, R. (2005). Prevention of relapse following cognitive therapy vs medications in moderate to severe depression. *Archives of general psychiatry, 62*(4), 417-422.

Holländare, F., Andersson, G., & Engström, I. (2010). *Comparison between BDI-II and MADRS-S administered on the Internet or on paper - are the psychometric properties the same?*Unpublished manuscript.

Holländare, F., Askerlund, A., Nieminen, A., & Engström, I. (2008). Can the BDI-II and MADRS-S be Transferred to Online Use Without Affecting their Psychometric Properties. *Electronic Journal of Applied Psychology, 4*(2).

Holländare, F., Johnsson, S., Randestad, M., Tillfors, M., Carlbring, P., Andersson, G., & Engström, I. (2010). *Internet based cognitive behaviour therapy can prevent relapse in major depression.*Unpublished manuscript.

Holma, I. A., Holma, K. M., Melartin, T. K., & Isometsa, E. T. (2008). Maintenance pharmacotherapy for recurrent major depressive disorder: 5-year follow-up study. *The British Journal of Psychiatry, 193*(2), 163-164.

Hopko, D. R., Lejuez, C. W., Ruggiero, K. J., & Eifert, G. H. (2003). Contemporary behavioral activation treatments for depression: procedures, principles, and progress. *Clinical Psychology Review, 23*(5), 699-717.

Houellebecq, M. (1994). *Extension du domaine de la lutte*. Paris: Maurice Nadeau.

Houston, T. K., Cooper, L. A., & Ford, D. E. (2002). Internet Support Groups for Depression: A 1-Year Prospective Cohort Study. *The American Journal of Psychiatry, 159*(12), 2062-2068.

Hunsley, J., & Lee, C. M. (2007). Research-Informed Benchmarks for Psychological Treatments: Efficacy Studies, Effectiveness Studies, and Beyond. *Professional Psychology - Research & Practice, 38*(1), 21-33.

Hurley, R. A., Fisher, R., & Taber, K. H. (2006). Sudden onset panic: epileptic aura or panic disorder? *The Journal of Neuropsychiatry and Clinical Neurosciences, 18*(4), 436-443.

Hybels, C. F., Pieper, C. F., & Blazer, D. G. (2009). The complex relationship between depressive symptoms and functional limitations in community-dwelling older adults: the impact of subthreshold depression. *Psychological Medicine, Forthcoming*(-1), 1-12.

Jacobson, N. S., Dobson, K. S., Truax, P. A., Addis, M. E., Koerner, K., Gollan, J. K., Gortner, E., & Prince, S. E. (1996). A component analysis of cognitive-behavioral treatment for depression. *Journal of Consulting and Clinical Psychology, 64*(2), 295-304.

Jacobson, N. S., & Gortner, E. T. (2000). Can depression be de-medicalized in the 21st century: scientific revolutions, counter-revolutions and the magnetic field of normal science. *Behaviour Research and Therapy, 38*(2), 103-117.

Jarrett, R. B., Eaves, G. G., Grannemann, B. D., & Rush, A. J. (1991). Clinical, cognitive, and demographic predictors of response to cognitive therapy for depression: a preliminary report. *Psychiatry Research, 37*(3), 245-260.

Johansson, R. (2009). TAYLOR - a randomized controlled trial of an individualized guided self-help treatment for depression, comorbid anxiety and sub-clinical symptoms. Unpublished Masters thesis. Linköping university.

Johnson, J. G., Cohen, P., Kasen, S., & Brook, J. S. (2006). Personality disorders evident by early adulthood and risk for anxiety disorders during middle adulthood. *Journal of Anxiety Disorders, 20*(4), 408-426.

Jorm, A. F. (2000). Does old age reduce the risk of anxiety and depression? A review of epidemiological studies across the adult life span. *Psychological Medicine, 30*(1), 11-22.

Judd, L. L., Akiskal, H. S., Maser, J. D., Zeller, P. J., Endicott, J., Coryell, W., Paulus, M. P., Kunovac, J. L., Leon, A. C., Mueller, T. I., Rice, J. A., & Keller, M. B. (1998). A prospective 12-year study of subsyndromal and syndromal depressive

symptoms in unipolar major depressive disorders. *Archives of general psychiatry, 55*(8), 694-700.

Kaltenthaler, E., Brazier, J., De Nigris, E., Tumur, I., Ferriter, M., Beverley, C., Parry, G., Rooney, G., & Sutcliffe, P. (2006). Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation. *Health technology assessment, 10*(33), iii, xi-xiv, 1-168.

Katerndahl, D., Burge, S., & Kellogg, N. (2005). Predictors of development of adult psychopathology in female victims of childhood sexual abuse. *Journal of nervous and mental disease, 193*(4), 258-264.

Kellner, M., Hirschmann, M., & Wiedemann, K. (1996). Panic attacks caused by temporal tumors: An exemplary new case and a review. *Depression and Anxiety, 4*(5), 243-245.

Kendler, K. S., & Gardner, C. O., Jr. (1998). Boundaries of major depression: an evaluation of DSM-IV criteria. *The American Journal of Psychiatry, 155*(2), 172-177.

Kendler, K. S., Gatz, M., Gardner, C. O., & Pedersen, N. L. (2006). A Swedish national twin study of lifetime major depression. *The American Journal of Psychiatry, 163*(1), 109-114.

Kendler, K. S., Kessler, R. C., Walters, E. E., MacLean, C., Neale, M. C., Heath, A. C., & Eaves, L. J. (1995). Stressful life events, genetic liability, and onset of an episode of major depression in women. *The American Journal of Psychiatry, 152*(6), 833-842.

Kenwright, M., Liness, S., & Marks, I. (2001). Reducing demands on clinicians by offering computer-aided self-help for phobia/panic. Feasibility study. *The British Journal of Psychiatry, 179*, 456-459.

Kenwright, M., Marks, I. M., Gega, L., & Mataix-Cols, D. (2004). Computer-aided self-help for phobia/panic via internet at home: a pilot study. *The British Journal of Psychiatry, 184*(5), 448-449.

Kessler, D., Lewis, G., Kaur, S., Wiles, N., King, M., Weich, S., Sharp, D. J., Araya, R., Hollinghurst, S., & Peters, T. J. (2009). Therapist-delivered Internet psychotherapy for depression in primary care: a randomised controlled trial. *Lancet, 374*(9690), 628-634.

Kessler, R. C., Andrews, G., Mroczek, D., Ustun, B., & Wittchen, H.-U. (1998). The World Health Organization Composite International Diagnostic Interview short-form (CIDI-SF). *International Journal of Methods in Psychiatric Research, 7*(4), 171-185.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., Rush, A. J., Walters, E. E., & Wang, P. S. (2003). The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *Journal of the American Medical Association, 289*(23), 3095-3105.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry, 62*(6), 593-602.

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry, 62*(6), 617-627.

Kessler, R. C., Chiu, W. T., Jin, R., Ruscio, A. M., Shear, K., & Walters, E. E. (2006). The epidemiology of panic attacks, panic disorder, and agoraphobia in the National Comorbidity Survey Replication. *Archives of general psychiatry, 63*(4), 415-424.

Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., Wittchen, H. U., & Kendler, K. S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Archives of general psychiatry, 51*(1), 8-19.

Kiropoulos, L. A., Klein, B., Austin, D. W., Gilson, K., Pier, C., Mitchell, J., & Ciechomski, L. (2008). Is internet-based CBT for panic disorder and agoraphobia as effective as face-to-face CBT? *Journal of Anxiety Disorders, 22*(8), 1273-1284.

Klein, B., Austin, D., Pier, C., Kiropoulos, L., Shandley, K., Mitchell, J., Gilson, K., & Ciechomski, L. (2009). Internet-Based Treatment for Panic Disorder: Does Frequency of Therapist Contact Make a Difference? *Cognitive Behaviour Therapy*, 1-14.

Klein, D. F. (1964). Delineation of Two Drug-Responsive Anxiety Syndromes. *Psychopharmacologia, 5*, 397-408.

Klein, M. H., Greist, J. H., & Van Cura, L. J. (1975). Computers and psychiatry. Promises to keep. *Archives of general psychiatry, 32*(7), 837-843.

Kocsis, J. H., Leon, A. C., Markowitz, J. C., Manber, R., Arnow, B., Klein, D. N., & Thase, M. E. (2009). Patient preference as a moderator of outcome for chronic forms of major depressive disorder treated with nefazodone, cognitive behavioral analysis system of psychotherapy, or their combination. *The journal of clinical psychiatry, 70*(3), 354-361.

Kraft, J. B., Slager, S. L., McGrath, P. J., & Hamilton, S. P. (2005). Sequence analysis of the serotonin transporter and associations with antidepressant response. *Biological psychiatry, 58*(5), 374-381.

Lavond, D. G., & Steinmetz, J. E. (2003). *Handbook of Classical Conditioning*. Norwell: Kluwer Academic Publischers.

Leichsenring, F. (2001). Comparative effects of short-term psychodynamic psychotherapy and cognitive-behavioral therapy in depression: a meta-analytic approach. *Clinical Psychology Review, 21*(3), 401-419.

Leichsenring, F. (2005). Are psychodynamic and psychoanalytic therapies effective?: A review of empirical data. *The International Journal of Psychoanalysis, 86*(3), 841-868.

Leichsenring, F., Rabung, S., & Leibing, E. (2004). The efficacy of short-term psychodynamic psychotherapy in specific psychiatric disorders: a meta-analysis. *Archives of general psychiatry, 61*(12), 1208-1216.

Leon, A. C., Olfson, M., Portera, L., Farber, L., & Sheehan, D. V. (1997). Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. *International Journal of Psychiatry in Medicine, 27*, 93–105.

Lesch, K. P. (2003). Neuroticism and Serotonin: A Developmental Genetic Perspective. In Plomin, R., DeFries, J. C., Craig, I. W. & McGuffin, P. (Eds.), *Behavioral Genetics in the Postgenomics Era*. Washington DC: American Psychiatric Association.

Lesch, K. P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., Benjamin, J., Muller, C. R., Hamer, D. H., & Murphy, D. L. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science, 274*(5292), 1527-1531.

Lewinsohn, P. M. (1974). A behavioral approach to depression. In Friedman, R. M. & Katz, M. M. (Eds.), *The psychology of depression: Contemporary theory and research*. New York: John Wiley & Sons.

Lewinsohn, P. M., Antonuccio, D. O., Steinmetz-Breckenridge, J. L., & Teri, L. (1984). *The Coping with Depression course: A psychoeducational intervention for unipolar depression*. Eugene, OR: Castalia Publishing.

Lewinsohn, P. M., Munoz, R. F., Youngren, M. A., & Zeiss, A. M. (1986). *Control Your Depression*. New York: Prentice Hall.

Levinson, D. F. (2006). The genetics of depression: a review. *Biological psychiatry, 60*(2), 84-92.

Linton, S. (2007). *Computer-Based Cognitive Behavioral Therapy for Anxiety Disorders or Depression*. Stockholm: SBU - The Swedish Council on Health Technology Assessment.

Lonsdorf, T. B., Rück, C., Bergström, J., Andersson, G., Öhman, A., Schalling, M., & Lindefors, N. (2009). The symptomatic profile of panic disorder is shaped by the 5-HTTLPR polymorphism. *Progress in neuro-psychopharmacology & biological psychiatry, 33*(8), 1479-1483.

Lonsdorf, T. B., Rück, C., Bergström, J., Öhman, A., Andersson, G., Lindefors, N., & Schalling, M. (2010). *The COMTval158met polymorphism affects symptom relief during exposure-based cognitive-behavioral treatment in panic disorder*.Unpublished manuscript.

Lonsdorf, T. B., Weike, A. I., Nikamo, P., Schalling, M., Hamm, A. O., & Ohman, A. (2009). Genetic gating of human fear learning and extinction: possible implications for gene-environment interaction in anxiety disorder. *Psychological science, 20*(2), 198-206.

Louie, A. K., Louie, E. K., & Lannon, R. A. (1992). Systemic hypertension associated with tricyclic antidepressant treatment in patients with panic disorder. *The American journal of cardiology, 70*(15), 1306-1309.

Lutz, W. (2003). Efficacy, effectiveness, and expected treatment response in psychotherapy. *Journal of Clinical Psychology, 59*(7), 745-750.

MacGillivray, S., Arroll, B., Hatcher, S., Ogston, S., Reid, I., Sullivan, F., Williams, B., & Crombie, I. (2003). Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis. *British Medical Journal, 326*(7397), 1014.

Mackinnon, A., Griffiths, K. M., & Christensen, H. (2008). Comparative randomised trial of online cognitive-behavioural therapy and an information website for depression: 12-month outcomes. *The British Journal of Psychiatry, 192*(2), 130-134.

Maier, W., Lichtermann, D., Minges, J., Oehrlein, A., & Franke, P. (1993). A controlled family study in panic disorder. *Journal of Psychiatric Research, 27 Suppl 1*, 79-87.

Markowitz, J. C., Svartberg, M., & Swartz, H. A. (1998). Is IPT time-limited psychodynamic psychotherapy? *The Journal of psychotherapy practice and research, 7*(3), 185-195.

Marks, I. M., Cavanagh, K., & Gega, L. (2007). *Hands-on help: computer-aided psychotherapy*. Hove: Psychology Press.

Martell, C. R., Addis, M. E., & Jacobson, N. S. (2001). *Depression in Context. Strategies for Guided Action.* New York: W. W. Norton.

Mattila-Evenden, M., Svanborg, P., Gustavsson, P., & Åsberg, M. (1996). Determinants of self-rating and expert rating concordance in psychiatric out-patients, using the affective subscales of the CPRS. *Acta Psychiatrica Scandinavica, 94*(6), 386-396.

Mavissakalian, M. R., & Perel, J. M. (1995). Imipramine treatment of panic disorder with agoraphobia: dose ranging and plasma level-response relationships. *The American Journal of Psychiatry, 152*(5), 673-682.

Mazzucchelli, T., Kane, R., & Rees, C. (2009). Behavioral Activation Treatments for Depression in Adults: A Meta-analysis and Review. *Clinical Psychology: Science and Practice, 16*(4), 383-411.

McBride, C., Atkinson, L., Quilty, L. C., & Bagby, R. M. (2006). Attachment as moderator of treatment outcome in major depression: a randomized control trial of interpersonal psychotherapy versus cognitive behavior therapy. *Journal of Consulting and Clinical Psychology, 74*(6), 1041-1054.

McCrone, P., Knapp, M., Proudfoot, J., Ryden, C., Cavanagh, K., Shapiro, D. A., Ilson, S., Gray, J. A., Goldberg, D., Mann, A., Marks, I., Everitt, B., & Tylee, A. (2004). Cost-effectiveness of computerised cognitive-behavioural therapy for anxiety and depression in primary care: randomised controlled trial. *The British Journal of Psychiatry, 185*, 55-62.

McGuffin, P., Rijsdijk, F., Andrew, M., Sham, P., Katz, R., & Cardno, A. (2003). The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Archives of general psychiatry, 60*(5), 497-502.

McKendree-Smith, N. L., Floyd, M., & Scogin, F. R. (2003). Self-administered treatments for depression: a review. *Journal of Clinical Psychology, 59*(3), 275-288.

Messer, S. B., & Warren, C. S. (1995). *Models of Brief Psychodynamic Therapy: A Comparative Approach*. New York: Guilford Press.

Meyer, B., Berger, T., Caspar, F., Beevers, C. G., Andersson, G., & Weiss, M. (2009). Effectiveness of a novel integrative online treatment for depression (Deprexis): randomized controlled trial. *Journal of medical Internet research, 11*(2), e15.

Milne, B. J., Caspi, A., Harrington, H., Poulton, R., Rutter, M., & Moffitt, T. E. (2009). Predictive value of family history on severity of illness: the case for depression, anxiety, alcohol dependence, and drug dependence. *Archives of general psychiatry, 66*(7), 738-747.

Milrod, B., Leon, A. C., Busch, F., Rudden, M., Schwalberg, M., Clarkin, J., Aronson, A., Singer, M., Turchin, W., Klass, E. T., Graf, E., Teres, J. J., & Shear, M. K. (2007). A randomized controlled clinical trial of psychoanalytic psychotherapy for panic disorder. *The American Journal of Psychiatry, 164*(2), 265-272.

Mitte, K. (2005). A meta-analysis of the efficacy of psycho- and pharmacotherapy in panic disorder with and without agoraphobia. *Journal of Affective Disorders, 88*(1), 27-45.

Mondimore, F. M., Zandi, P. P., Mackinnon, D. F., McInnis, M. G., Miller, E. B., Crowe, R. P., Scheftner, W. A., Marta, D. H., Weissman, M. M., Levinson, D. F., Murphy-Ebenez, K. P., Depaulo, J. R., Jr., & Potash, J. B. (2006). Familial aggregation of illness chronicity in recurrent, early-onset major depression pedigrees. *The American Journal of Psychiatry, 163*(9), 1554-1560.

Montgomery, S., & Åsberg, M. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry, 134*(4), 382-389.

Munafo, M. R., Brown, S. M., & Hariri, A. R. (2008). Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. *Biological psychiatry, 63*(9), 852-857.

Munafo, M. R., Freimer, N. B., Ng, W., Ophoff, R., Veijola, J., Miettunen, J., Jarvelin, M. R., Taanila, A., & Flint, J. (2009). 5-HTTLPR genotype and anxiety-related personality traits: a meta-analysis and new data. *American journal of medical genetics. Part B, Neuropsychiatric genetics, 150B*(2), 271-281.

Murray, C. J., & Lopez, A. D. (1997). Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet, 349*(9064), 1498-1504.

National Board of Health and Welfare (2010). National Guidelines for the Treatment of Depression and Anxiety Disorders. Stockholm: The National Board of Health and Welfare.

Newell, D. J. (1992). Intention-to-treat analysis: implications for quantitative and qualitative research. *International Journal of Epidemiology, 21*(5), 837-841.

Nocon, A., Wittchen, H.-U., Beesdo, K., Br¸ckl, T., Hofler, M., Pfister, H., Zimmermann, P., & Lieb, R. (2008). Differential familial liability of panic disorder and agoraphobia. *Depression and Anxiety, 25*(5), 422-434.

Nordgreen, T., Standal, B., Mannes, H., Haug, T., Sivertsen, B., Carlbring, P., Andersson, G., Heiervang, E., & Havik, O. E. (2010). Guided self-help via internet for panic disorder: Dissemination across countries. *Computers in Human Behavior, In Press*.

Nordin, S., Carlbring, P., Cuijpers, P., & Andersson, G. (2010). Expanding the Limits of Bibliotherapy for Panic Disorder: Randomized Trial of Self-Help Without Support but With a Clear Deadline. *Behavior Therapy, In Press.*

Norton, P. J., & Price, E. C. (2007). A meta-analytic review of adult cognitive-behavioral treatment outcome across the anxiety disorders. *Journal of nervous and mental disease, 195*(6), 521-531.

Ozkan, M., & Altindag, A. (2005). Comorbid personality disorders in subjects with panic disorder: do personality disorders increase clinical severity? *Comprehensive Psychiatry, 46*(1), 20-26.

Palmqvist, B. r., Carlbring, P., & Andersson, G. (2007). Internet-delivered treatments with or without therapist input: does the therapist factor have implications for efficacy and cost? *Expert Review of Pharmacoeconomics & Outcomes Research, 7*(3), 291-297.

Patten, S. B. (2003). Prevention of depressive symptoms through the use of distance technologies. *Psychiatric Services, 54*(3), 396-398.

Pavlov, I. P. (1927). *Conditioned reflexes*. Oxford: Oxford University Press.

Paxling, B., Almlöv, J., Dahlin, M., Airola, K., Holmer, E., Eriksson, O., Norgren, A., Roch-Norlund, P., Östman, G., Breitholtz, E., Silverberg, F., Carlbring, P., & Andersson, G. (2009). *Internet delivered cognitive behavior therapy vs. Internet delivered psychoanalytic therapy for generalized anxiety disorder - which is more effective?* Paper presented at the First International E-Mental Health Summit.

Perini, S., Titov, N., & Andrews, G. (2009). Clinician-assisted Internet-based treatment is effective for depression: randomized controlled trial. *Australian and New Zealand journal of psychiatry, 43*(6), 571-578.

Pezawas, L., Meyer-Lindenberg, A., Drabant, E. M., Verchinski, B. A., Munoz, K. E., Kolachana, B. S., Egan, M. F., Mattay, V. S., Hariri, A. R., & Weinberger, D. R. (2005). 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nature Neuroscience, 8*(6), 828-834.

Pine, D. S., Cohen, P., Johnson, J. G., & Brook, J. S. (2002). Adolescent life events as predictors of adult depression. *Journal of Affective Disorders, 68*(1), 49-57.

Proudfoot, J., Ryden, C., Everitt, B., Shapiro, D. A., Goldberg, D., Mann, A., Tylee, A., Marks, I., & Gray, J. A. (2004). Clinical efficacy of computerised cognitive-behavioural therapy for anxiety and depression in primary care: randomised controlled trial. *The British Journal of Psychiatry, 185*, 46-54.

Ramnerö, J., & Törneke, N. (2008). *The ABCs of Human Behavior: Behavioral Principles for the Practicing Clinician.* Oakland: New Harbinger Publications.

Ramnerö, J., & Öst, L. G. (2004). Prediction of outcome in the behavioural treatment of panic disorder with agoraphobia. *Cognitive Behaviour Therapy, 33*(4), 176-180.

Ramnerö, J., & Öst, L. G. (2007). Panic and avoidance in panic disorder with agoraphobia: clinical relevance of change in different aspects of the disorder. *Journal of Behavior Therapy and Experimental Psychiatry, 38*(1), 29-39.

Reinecke, M. A., Ryan, N. E., & DuBois, D. L. (1998). Cognitive-behavioral therapy of depression and depressive symptoms during adolescence: a review and meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry, 37*(1), 26-34.

Reiss, S., Peterson, R. A., Gursky, D. M., & McNally, R. J. (1986). Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behaviour Research and Therapy, 24*(1), 1-8.

Richards, D. A., Lovell, K., & McEvoy, P. (2003). Access and effectiveness in psychological therapies: self-help as a routine health technology. *Health & social care in the community, 11*(2), 175-182.

Richards, J., Klein, B., & Carlbring, P. (2003). Internet-based treatment for panic disorder. *Cognitive Behaviour Therapy, 32*(3), 125-135.

Riederer, P., Lachenmayer, L., & Laux, G. (2004). Clinical applications of MAO-inhibitors. *Current Medicinal Chemistry, 11*(15), 2033-2043.

Risch, N., Herrell, R., Lehner, T., Liang, K. Y., Eaves, L., Hoh, J., Griem, A., Kovacs, M., Ott, J., & Merikangas, K. R. (2009). Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. *Journal of the American Medical Association, 301*(23), 2462-2471.

Rosen, G. M. (1987). Self-help treatment books and the commercialization of psychotherapy. *American psychologist, 42*(1), 46-51.

Rosen, G. M., Glasgow, R. E., & Barrera, M., Jr. (1976). A controlled study to assess the clinical efficacy of totally self-administered systematic desensitization. *Journal of Consulting and Clinical Psychology, 44*(2), 208-217.

Rosenberg, L. B., Whang, W., Shimbo, D., Shah, A., Shapiro, P. A., & Davidson, K. W. (2010). Exposure to tricyclic antidepressants is associated with an increased risk of incident CHD events in a population-based study. *International journal of cardiology, In Press*.

Rosenthal, R. (1991). *Meta-Analytic Procedures for Social Research.* Newbury Park: Sage.

Rosenthal, R., & Rosnow, R. L. (1991). *Essentials of behavioral research: Methods and data analysis*. New York: McGraw Hill.

Roy-Byrne, P. P., & Cowley, D. S. (2002). Pharmacologic treatment for panic disorder, generalized anxiety disorder, specific phobia and social anxiety disorders. In Nathan, P. & Gorman, J. M. (Eds.), *A guide to treatments that work* (2nd ed., pp. 337–365). New York: Oxford University Press.

Roy-Byrne, P. P., Stang, P., Wittchen, H. U., Ustun, B., Walters, E. E., & Kessler, R. C. (2000). Lifetime panic-depression comorbidity in the National Comorbidity Survey. Association with symptoms, impairment, course and help-seeking. *The British Journal of Psychiatry, 176*, 229-235.

Ruwaard, J., Schrieken, B., Schrijver, M., Broeksteeg, J., Dekker, J., Vermeulen, H., & Lange, A. (2009). Standardized web-based cognitive behavioural therapy of mild to moderate depression: a randomized controlled trial with a long-term follow-up. *Cognitive Behaviour Therapy, 38*(4), 206-221.

Sackett, D. L., Rosenberg, W. M., Gray, J. A., Haynes, R. B., & Richardson, W. S. (1996). Evidence based medicine: what it is and what it isn't. *British Medical Journal, 312*(7023), 71-72.

Sandell, R. (1987). Assessing the effects of psychotherapy. IV. The incompatibility between the logic of the experiment and the nature of psychotherapy. *Psychotherapy and Psychosomatics, 47*(1), 53-58.

Schneider, A. J., Mataix-Cols, D., Marks, I. M., & Bachofen, M. (2005). Internet-guided self-help with or without exposure therapy for phobic and panic disorders. *Psychotherapy and Psychosomatics, 74*(3), 154-164.

Schoenwald, S. K., & Hoagwood, K. (2001). Effectiveness, transportability, and dissemination of interventions: what matters when? *Psychiatric Services, 52*(9), 1190-1197.

Schweizer, E., Pohl, R., Balon, R., Fox, I., Rickels, K., & Yeragani, V. K. (1990). Lorazepam vs. alprazolam in the treatment of panic disorder. *Pharmacopsychiatry, 23*(2), 90-93.

Scogin, F., Floyd, M., Jamison, C., Ackerson, J., Landreville, P., & Bissonnette, L. (1996). Negative outcomes: what is the evidence on self-administered treatments? *Journal of Consulting and Clinical Psychology, 64*(5), 1086-1089.

Shadish, W. R., Matt, G. E., Navarro, A. M., & Phillips, G. (2000). The effects of psychological therapies under clinically representative conditions: a meta-analysis. *Psychological bulletin, 126*(4), 512-529.

Shadish, W. R., Matt, G. E., Navarro, A. M., Siegle, G., Crits-Christoph, P., Hazelrigg, M. D., Jorm, A. F., Lyons, L. C., Nietzel, M. T., Prout, H. T., Robinson, L., Smith, M. L., Svartberg, M., & Weiss, B. (1997). Evidence that therapy works in clinically representative conditions. *Journal of Consulting and Clinical Psychology, 65*(3), 355-365.

Shandley, K., Austin, D. W., Klein, B., Pier, C., Schattner, P., Pierce, D., & Wade, V. (2008). Therapist-assisted, Internet-based treatment for panic disorder: can general practitioners achieve comparable patient outcomes to psychologists? *Journal of medical Internet research, 10*(2), e14.

Shear, M. K., Brown, T. A., Barlow, D. H., Money, R., Sholomskas, D. E., Woods, S. W., Gorman, J. M., & Papp, L. A. (1997). Multicenter collaborative panic disorder severity scale. *The American Journal of Psychiatry, 154*(11), 1571-1575.

Sheehan, D. V. (1984). The treatment of panic and phobic disorders. In Bernstein, J. C. (Ed.), *Clinical Psychopharmacology* (2nd ed.). Boston: John Wright PSG.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The journal of clinical psychiatry, 59 Suppl 20*, 22-33;quiz 34-57.

Shih, R. A., Belmonte, P. L., & Zandi, P. P. (2004). A review of the evidence from family, twin and adoption studies for a genetic contribution to adult psychiatric disorders. *International Review of Psychiatry, 16*(4), 260-283.

Siev, J., & Chambless, D. L. (2007). Specificity of treatment effects: cognitive therapy and relaxation for generalized anxiety and panic disorders. *Journal of Consulting and Clinical Psychology, 75*(4), 513-522.

Silverberg, F. (2005). *Make the Leap: A Practical Guide to Breaking the Patterns That Hold You Back*. New York: Marlowe & Company.

Simon, N. M., Blacker, D., Korbly, N. B., Sharma, S. G., Worthington, J. J., Otto, M. W., & Pollack, M. H. (2002). Hypothyroidism and hyperthyroidism in anxiety disorders revisited: new data and literature review. *Journal of Affective Disorders, 69*(1-3), 209-217.

Singareddy, R., & Uhde, T. W. (2009). Nocturnal sleep panic and depression: relationship to subjective sleep in panic disorder. *Journal of Affective Disorders, 112*(1-3), 262-266.

Skinner, B. F. (1965). *Science and Human Behavior*. New York: The Free Press.

Skinner, B. F. (1975). The steep and thorny way to a science of behavior. *American psychologist, 30*(1), 42-49.

Skinner, B. F. (1988). The operant side of behavior therapy. *Journal of Behavior Therapy and Experimental Psychiatry, 19*(3), 171-179.

Smoller, J. W., & Tsuang, M. T. (1998). Panic and phobic anxiety: defining phenotypes for genetic studies. *The American Journal of Psychiatry, 155*(9), 1152-1162.

Solomon, D. A., Keller, M. B., Leon, A. C., Mueller, T. I., Lavori, P. W., Shea, M. T., Coryell, W., Warshaw, M., Turvey, C., Maser, J. D., & Endicott, J. (2000). Multiple recurrences of major depressive disorder. *The American Journal of Psychiatry, 157*(2), 229-233.

Spek, V., Cuijpers, P., Nyklicek, I., Riper, H., Keyzer, J., & Pop, V. (2007). Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. *Psychological Medicine, 37*(3), 319-328.

Spek, V., Cuijpers, P., Nyklicek, I., Smits, N., Riper, H., Keyzer, J., & Pop, V. (2008). One-year follow-up results of a randomized controlled clinical trial on internet-based cognitive behavioural therapy for subthreshold depression in people over 50 years. *Psychological Medicine, 38*(5), 635-639.

Spek, V., Nyklicek, I., Cuijpers, P., & Pop, V. (2008). Predictors of outcome of group and internet-based cognitive behavior therapy. *Journal of Affective Disorders, 105*(1-3), 137-145.

Spek, V., Nyklicek, I., Smits, N., Cuijpers, P., Riper, H., Keyzer, J., & Pop, V. (2007). Internet-based cognitive behavioural therapy for subthreshold depression in people over 50 years old: a randomized controlled clinical trial. *Psychological Medicine, 37*(12), 1797-1806.

Stahl, S. M. (1998). Basic psychopharmacology of antidepressants, part 1: Antidepressants have seven distinct mechanisms of action. *The journal of clinical psychiatry, 59 Suppl 4*, 5-14.

Steketee, G., & Chambless, D. L. (1992). Methodological issues in prediction of treatment outcome. *Clinical Psychology Review, 12*(4), 387-400.

Stewart, R. E., & Chambless, D. L. (2009). Cognitive-behavioral therapy for adult anxiety disorders in clinical practice: a meta-analysis of effectiveness studies. *Journal of Consulting and Clinical Psychology, 77*(4), 595-606.

Strug, L. J., Suresh, R., Fyer, A. J., Talati, A., Adams, P. B., Li, W., Hodge, S. E., Gilliam, T. C., & Weissman, M. M. (2010). Panic disorder is associated with the serotonin transporter gene (SLC6A4) but not the promoter region (5-HTTLPR). *Molecular Psychiatry, 15*(2), 166-176.

Ström, L., Pettersson, R., & Andersson, G. (2004). Internet-Based Treatment for Insomnia: A Controlled Evaluation. *Journal of Consulting and Clinical Psychology, 72*(1), 113-120.

Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic epidemiology of major depression: review and meta-analysis. *The American Journal of Psychiatry, 157*(10), 1552-1562.

Svanborg, P., & Åsberg, M. (2001). A comparison between the Beck Depression Inventory (BDI) and the self-rating version of the Montgomery Åsberg Depression Rating Scale (MADRS). *Journal of Affective Disorders, 64*(2-3), 203-216.

Sweet, R. A., Brown, E. J., Heimberg, R. G., Ciafre, L., Scanga, D. M., Cornelius, J. R., Dube, S., Forsyth, K. M., & Holt, C. S. (1995). Monoamine oxidase inhibitor dietary restrictions: what are we asking patients to give up? *The journal of clinical psychiatry, 56*(5), 196-201.

Taylor, S. (2000). *Understanding and treating panic disorder. Cognitive-behavioral approaches.* Chichester: John Wiley & Sons.

Thase, M. E. (2007). Recognition and diagnosis of atypical depression. *The journal of clinical psychiatry, 68 Suppl 8*, 11-16.

van Balkom, A. J., Bakker, A., Spinhoven, P., Blaauw, B. M., Smeenk, S., & Ruesink, B. (1997). A meta-analysis of the treatment of panic disorder with or without agoraphobia: a comparison of psychopharmacological, cognitive-behavioral, and combination treatments. *Journal of nervous and mental disease, 185*(8), 510-516.

van Straten, A., Cuijpers, P., & Smits, N. (2008). Effectiveness of a web-based self-help intervention for symptoms of depression, anxiety, and stress: randomized controlled trial. *Journal of medical Internet research, 10*(1), e7.

Vernmark, K., Lenndin, J., Bjärehed, J., Carlsson, M., Karlsson, J., Öberg, J., Carlbring, P., Eriksson, T., & Andersson, G. (2010). Internet administered guided self-help versus individualized e-mail therapy: A randomized trial of two versions of CBT for major depression. *Behaviour Research and Therapy, In Press.*

Vittengl, J. R., Clark, L. A., Dunn, T. W., & Jarrett, R. B. (2007). Reducing relapse and recurrence in unipolar depression: a comparative meta-analysis of cognitive-behavioral therapy's effects. *Journal of Consulting and Clinical Psychology, 75*(3), 475-488.

Walters, K., Rait, G., Petersen, I., Williams, R., & Nazareth, I. (2008). Panic disorder and risk of new onset coronary heart disease, acute myocardial infarction, and cardiac mortality: cohort study using the general practice research database. *European Heart Journal, 29*(24), 2981-2988.

Wampold, B. E. (2001). *The great psychotherapy debate. Models, methods, and findings*. Mahaw, New Jersey: Lawrence Erlbaum.

Wang, H., & Zhao, H. (2006). Estimating incremental cost-effectiveness ratios and their confidence intervals with differentially censored data. *Biometrics, 62*(2), 570-575.

Warmerdam, L., van Straten, A., Twisk, J., Riper, H., & Cuijpers, P. (2008). Internet-based treatment for adults with depressive symptoms: randomized controlled trial. *Journal of medical Internet research, 10*(4), e44.

Weizenbaum, J. (1966). ELIZA - A Computer Program For the Study of Natural Language Communication Between Man And Machine. *Communications of the ACM, 9*(1), 36–45.

Westen, D., & Morrison, K. (2001). A multidimensional meta-analysis of treatments for depression, panic, and generalized anxiety disorder: an empirical examination of the status of empirically supported therapies. *Journal of Consulting and Clinical Psychology, 69*(6), 875-899.

Westen, D., Novotny, C. M., & Thompson-Brenner, H. (2004). The empirical status of empirically supported psychotherapies: assumptions, findings, and reporting in controlled clinical trials. *Psychological bulletin, 130*(4), 631-663.

Wittchen, H. U., Nocon, A., Beesdo, K., Pine, D. S., Hofler, M., Lieb, R., & Gloster, A. T. (2008). Agoraphobia and panic. Prospective-longitudinal relations suggest a rethinking of diagnostic concepts. *Psychotherapy and Psychosomatics, 77*(3), 147-157.

World Health Organization (2002). *The World Health Report 2002: Reducing Risks, Promoting Healthy Life*. Geneva: World Health Organization.

Yonkers, K. A., Bruce, S. E., Dyck, I. R., & Keller, M. B. (2003). Chronicity, relapse, and illness--course of panic disorder, social phobia, and generalized anxiety disorder: findings in men and women from 8 years of follow-up. *Depression and anxiety, 17*(3), 173-179.

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica, 67*(6), 361-370.

Öst, L. G. (1987). Applied relaxation: description of a coping technique and review of controlled studies. *Behaviour Research and Therapy, 25*(5), 397-409.

Öst, L. G., Thulin, U., & Ramnerö, J. (2004). Cognitive behavior therapy vs exposure in vivo in the treatment of panic disorder with agoraphobia. *Behaviour Research and Therapy, 42*(10), 1105-1127.

Öst, L. G., & Westling, B. E. (1995). Applied relaxation vs cognitive behavior therapy in the treatment of panic disorder. *Behaviour Research and Therapy, 33*(2), 145-158.

Öst, L. G., Westling, B. E., & Hellström, K. (1993). Applied relaxation, exposure in vivo and cognitive methods in the treatment of panic disorder with agoraphobia. *Behaviour Research and Therapy, 31*(4), 383-394.