Managing Depression via the Internet
To Ebba and Ester
Managing Depression via the Internet
– self-report measures, treatment & relapse prevention
Abstract


Cognitive behaviour therapy (CBT) is an effective treatment for depression but access is limited. One way of increasing access is to offer CBT via the Internet. In Study I, guided Internet-based CBT was found to have a large effect on depressive symptoms compared to taking part in an online discussion group. Approximately two hours were spent on guiding each patient and the large effect found differs from previous studies that showed smaller effects, probably due to lack of guidance. The intervention had no effect on the participants’ quality of life but significantly decreased their level of anxiety.

Internet-based versions of self-report measures can be more practical and efficient than paper versions. However, before implementation, evidence of psychometrical equivalence to the paper versions should be available. This was tested in Studies II and III for the Montgomery-Åsberg Depression Rating Scale – Self-rated (MADRS-S) and the Beck Depression Inventory – Second Edition (BDI-II). When the full scales were investigated, equivalent psychometric properties were found in the two versions of the MADRS-S and BDI-II. However, in the Internet-version of the BDI-II, a lower score was found for the question about suicidality and the difference was statistically significant. Although the difference was small, this indicates that suicidality might be underestimated when using the Internet-based BDI-II.

As the long-term prognosis after treatment for depression is poor, in Study IV we investigated the possibility of delivering CBT-based relapse prevention via the Internet. The results revealed that fewer participants in the intervention group experienced a relapse compared to the control group and that the time spent on guiding each participant was approximately 2.5 hours. A trend towards a higher remission rate was found in the CBT group at the six-month follow-up and a reduction of depressive symptoms was associated with a lowered risk of relapse. CBT-based relapse prevention via the Internet can potentially be made available to large numbers of patients, thus improving their prognosis.

The Internet increases the possibilities for health care providers in the management of depression.

Keywords: Internet, depression, cognitive behaviour therapy, self-report measures, relapse prevention

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LIST OF PAPERS
This thesis is based on the following original papers, which will be referred to in the text by their Roman numerals:


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**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADM</td>
<td>Antidepressant medication</td>
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<td>BA</td>
<td>Behavioural activation</td>
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<td>BAI</td>
<td>Beck Anxiety Inventory</td>
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<tr>
<td>BDI-II</td>
<td>Beck Depression Inventory – Second Edition</td>
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<tr>
<td>BT</td>
<td>Behaviour therapy</td>
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<td>CBT</td>
<td>Cognitive behaviour therapy</td>
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<td>CM</td>
<td>Clinical management</td>
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<td>CT</td>
<td>Cognitive therapy</td>
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<tr>
<td>DSM-IV</td>
<td>Diagnostic &amp; Statistical Manual of Mental Disorders (4 ed.)</td>
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<tr>
<td>ECT</td>
<td>Electroconvulsive therapy</td>
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<tr>
<td>GP</td>
<td>General practitioner</td>
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<td>HDRS</td>
<td>Hamilton Depression Rating Scale</td>
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<td>IPT</td>
<td>Interpersonal psychotherapy</td>
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<tr>
<td>ISPOR</td>
<td>International Society for Pharmacoeconomics and Outcomes Research</td>
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<td>ITC</td>
<td>International Test Commission</td>
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<tr>
<td>MADRS-S</td>
<td>Montgomery-Åsberg Depression Rating Scale – Self rated</td>
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<td>MAOI</td>
<td>Monoamine oxidase inhibitors</td>
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<tr>
<td>MBCT</td>
<td>Mindfulness-based cognitive therapy</td>
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<td>MDD</td>
<td>Major depressive disorder</td>
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<td>PST</td>
<td>Problem-solving therapy</td>
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<td>QoLI</td>
<td>Quality of Life Inventory</td>
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<tr>
<td>SCID-I</td>
<td>Structured Clinical Interview for DSM-IV axis I Disorders</td>
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<tr>
<td>SMS</td>
<td>Short message service</td>
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<tr>
<td>SNRI</td>
<td>Serotonin norepinephrine reuptake inhibitors</td>
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<td>SSRI</td>
<td>Selective serotonin reuptake inhibitors</td>
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<tr>
<td>TAU</td>
<td>Treatment as usual</td>
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<td>TCA</td>
<td>Tricyclic antidepressants</td>
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<td>WBT</td>
<td>Well-being therapy</td>
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<tr>
<td>WHOQOL</td>
<td>World Health Organization Quality Of Life</td>
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INTRODUCTION

Background

“When I rise my breakfast is solitary, the black dog waits to share it, from breakfast to dinner he continues barking, […]

After dinner, what remains but to count the clock, and hope for that sleep which I can scarce expect.

Night comes at last, and some hours of restlessness and confusion bring me again to a day of solitude. What shall exclude the black dog from an habitation like this?”

Dr Samuel Johnson (Chapman 1952)

Throughout history, a variety of terms have been used to label the experience of persistent low mood and the loss of interest in activities. If “the black dog” is one of the more poetic examples, melancholia has surely been the most persistent. Actually, melancholia was the customary term for experiences of low mood and anhedonia for more than 2000 years (Davison 2006), and although it has been argued that “depression” is a narrower concept (Radden 2003) it clearly fits within the older concept of melancholia. Whatever the term, the descriptions of the symptoms enable us to trace this phenomenon back through history. It seems that this problem has always accompanied humans although the theories about aetiology as well as the suggested remedies have changed dramatically over the centuries (Hammer 2004).

Today, the accepted psychiatric term is major depressive disorder (MDD). MDD, also refered to as unipolar depression, is one of the most prevalent psychiatric problems and although there are several effective treatments and forms of relapse prophylaxis many patients receive neither (Kessler et al. 2003). Some people suffering from depression do not receive treatment because they do not seek help (ibid.), but when it comes to providing cognitive behaviour therapy (CBT) to patients, the shortage of trained therapists limits access. This thesis explores one possible way of making CBT interventions accessible to more patients by means of the Internet.

The overarching question in this thesis is whether clinicians can use the Internet to manage cases of depression. The aim was to explore if Internet-
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Background

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The overarching question in this thesis is whether clinicians can use the Internet to manage cases of depression. The aim was to explore if Internet-
based solutions can be a complement for health care providers in measuring, treating and preventing relapse in some sufferers of depression. The included studies investigated the possibilities of Internet-based cognitive behaviour therapy for depression, Internet-based self-report measures of depressive symptoms and Internet-based relapse prevention for sufferers of partially remitted depression. The population of interest was adults suffering from unipolar depression or depressive symptoms.

**Depression**

**Symptoms**

In addition to low mood and anhedonia, the typical symptoms of depression are weight loss or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, inappropriate guilt, concentration difficulties and suicidal ideation. The clinician typically specifies the severity of an episode along the continuum: mild, moderate, severe without psychotic features and severe with psychotic features. The degree of remission can also be specified, as well as the chronicity. An episode is considered chronic if the patient has constantly fulfilled the diagnostic criteria for two years. Other possible specifications of a depressive episode are the presence of catatonic features, postpartum onset and the addition of melancholia, which includes inability to find pleasure in positive things (American Psychiatric Association 2000).

**Epidemiology**

Major depression is a prevalent disorder, and according to the often cited National Comorbidity Survey, it afflicts about 17% of the population sometime during their life (Kessler et al. 1994). When the study was replicated a decade later, the result remained essentially unchanged with an estimate of 16.2% (Kessler et al. 2003). However, it has been argued that most prevalence studies underestimate the true number of individuals who experience depression, mainly because of their retrospective design. Citing ongoing prospective studies, Andrews et al. (2005) estimate that half of the population can expect one or more depressive episodes during their life. This view is supported by Moffit et al. (2010), who collects data prospectively on psychiatric problems in a large cohort. About 40% of their cohort had experienced depression by the age of 32, which is about twice as many (at the same age) as in the retrospective study by Kessler (2003). In the rigorous prospective Lundby study, the risk of suffering a depressive disorder for the first time until 70 years of age was 27% in men and 45% in women (Rorsman et al. 1990). The proportion of the
population suffering from depression at any given time has been estimated at 7.3% in a study by Hodiamont et al. (1987).

Depression is not only prevalent, but also debilitating for the sufferers. Kessler et al. (2003) found that 87% of those who fulfilled the criteria for MDD also experienced a role impairment that was at least moderate, at home, at work, socially or in relationships.

Depression is not evenly distributed across genders, and one of the most consistent epidemiological findings is that women are more often afflicted than men (Kessler et al. 2003; Kessler et al. 1994; Rorsman et al. 1990). A common estimation is that women have twice the risk of MDD compared to men. For example, Kessler (1994) found that 21.3% of all women and 12.7% of all men will experience depression during their lifetime. However, this difference between men and women is largest regarding mild and moderate cases, while the difference in the risk of developing a severe episode of depression seems smaller (Kessler et al. 2003; Rorsman et al. 1990).

Depression frequently occurs together with other problems, and a common psychiatric comorbidity has been found to be anxiety disorders. In fact, Kessler et al. (2003) found that a majority of cases (almost 60%) had a comorbid anxiety disorder, while a substance abuse disorder was identified in 24% of cases.

**Course**
The mean episode duration has been reported to be 16 weeks with fairly similar length in cases showing mild, moderate and severe symptoms, but with a clearly longer duration (23 weeks) in cases classified as having very severe symptoms (Kessler et al. 2003). Similar results were found by Angst et al. (2003) who report 23 weeks to be the mean episode duration in a sample that was hospitalized at least once for MDD.

For some who suffer an episode of MDD it is a one time occurrence, but for many others it becomes a recurrent disorder. The proportion of the afflicted that suffer a relapse in MDD varies between different study samples and the selection method influences this risk estimation. In a study by Mattisson et al. (2007), all cases of depressive disorders found in a specified geographic area of Sweden were followed over five decades. About 40% of the whole sample suffered a relapse, ranging from approximately 20% in those followed for ten years after their first episode.
to around 75% recurrence in those followed for 50 years. In another study, the proportion that relapsed was calculated to be about 45% two years after recovery, 60% after four years and 85% after 15 years (Mueller et al. 1999). The risk of relapse is thus highest shortly after recovery and as the time in remission increases, the risk of relapse decreases (Solomon et al. 2000). The prognosis seems to worsen with every successive relapse (Kessing et al. 2004; Mueller et al. 1999) and one estimation is that for every new episode, the risk of relapse increases by 16% (Solomon et al. 2000). The time until relapse seems to decrease with every new episode, which was well illustrated when a sample of fairly severe cases mostly comprising inpatients was followed for ten years. While the median time before the first relapse was almost three years, it gradually decreased so that the median time between the end of the 4th episode and the onset of the 5th relapse was a little over one year (ibid.). Not only do the episodes seem to become more frequent as the number suffered for an individual increases, but there is also an indication that the severity increases. In a study of a national case register by Kessing (2008), the cases considered severe were 25% for all first episodes, over 40% for fifth episodes and about 50% for the fifteenth episode.

A particularly interesting result in the above-mentioned study by Mattinsson et al. (2007) is that women and men seem to have a similar risk of relapse. The same result was found by Angst et al. (2003), possibly indicating that although women have a higher risk of falling ill with their first episode of depression, both genders have an equal risk of relapse after the first episode, and thus the course of illness is very similar. In a study by Mueller et al. (1999) however, it was estimated that women have a 43% higher risk of relapse, so the findings are inconclusive.

During a 23 year follow up of persons afflicted by depression, the median number of episodes experienced was four (Angst & Preisig 1995a). However, the persons in the study were fairly severe cases since all were diagnosed with “endogenous” depression.

Depression is associated with elevated risk of suicide, and in the follow up study by Mattinsson et al. (2007) 5% committed suicide (10% of males and 2% of females). Apart from gender, episode severity was the strongest predictor of suicide. Higher suicide rates have been found in samples with more severe symptoms, for example 15% during a 27 year follow up after hospitalization for depression (Angst & Preisig 1995b).
Treatment

Many treatments have been shown to be effective for MDD and different pharmacological agents are a common first line treatment. No group of antidepressant medication (ADM) stands out as the most effective overall, although some agents have shown better outcomes in subgroups of patients. There are considerable differences in side effects from the different groups of antidepressants. Largely because of their high tolerability, selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are considered the first choice (American Psychiatric Association 2010). Other groups of antidepressant medication are tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Another physical antidepressant treatment is electroconvulsive therapy (ECT), which is the most effective remedy for severe depression. It is often used in severe cases after medication has been unsuccessful or when a severe episode includes psychotic symptoms (ibid.). The physical activity level has been found to affect depression although the empirical support is weaker compared to pharmaco- and psychotherapy (Harvey et al. 2010).

Many forms of psychotherapy have also been used for treating depression, and in a meta-analysis (Cuijpers et al. 2008), the authors compared the effect of no less than seven, although they excluded others that had been studied in less than five randomized controlled trials. As only small differences were found between the various treatments, the overall impression was that, with few exceptions, they were equally effective. Some of the more widely used and most often studied forms of psychotherapy for depression are cognitive behaviour therapy (CBT), psychodynamic psychotherapy and interpersonal psychotherapy (IPT).

IPT focuses on the patients’ relationships and the impact of interpersonal issues on depression. The aim is to decrease relationship problems and the therapist has an active role. IPT can be administered as group therapy or individually and is a highly structured, manualised treatment (Weissman et al. 2007). It has been found to be equally effective as ADM in the treatment of mild to moderate depression (Elkin et al. 1989) and in a recent meta analysis IPT was shown to be equally effective compared to other forms of psychotherapy (Cuijpers et al. 2011). Psychodynamic psychotherapy is primarily aimed at helping the patient become aware of and understand repeated intrapsychic and intrapersonal conflicts. It is assumed that historical relationships, childhood and previous un-resolved conflicts affect a patient’s present life situation, and wishes as well as
Cognitive behaviour therapy (CBT) is yet another form of psychological treatment that has been shown to be effective in the treatment of depression (Cuijpers et al. 2008). A large proportion of the self-help literature pertaining to depression is based on CBT, and since this literature inspired the growth of Internet-based treatments, CBT is of particular interest in this thesis and described below in greater detail.

Cognitive behaviour therapy
Cognitive behaviour therapy for depression emanates from two different theories about the underlying mechanism that causes and maintains it, one emphasizing the importance of the function of behaviour and the other focusing on the content of cognition. Behaviour therapy (BT) for depression builds on the work of Charles Ferster and his publication “A Functional Analysis of Depression” (Ferster 1973), and was further developed by Peter Lewinsohn (Lewinsohn et al. 1986) and later gave rise to behavioural activation (BA) (Martell et al. 2001). Cognitive therapy (CT) was developed by Aaron Beck and originally described in his book Cognitive Therapy of Depression (Beck et al. 1979). Cognitive behaviour therapy is a combination of interventions from behaviour therapy and cognitive therapy, and the efficacy of CBT for depression has been studied in over 75 clinical trials for more than 30 years. The evidence from a large review of meta-analyses suggests that CBT has a large effect compared to waiting list and placebo (Butler et al. 2006). However, the methods used in some of the studies have been the subject of criticism and a meta-analysis has been conducted that only included studies controlling for non-specific effects with placebo or a control psychological intervention as a comparison group. Significant effects of CBT on depression were still found, albeit smaller (Lynch et al. 2010). Another meta-analysis only included studies with blind assessment of outcome and found significant effects of CBT on depression although smaller compared to studies with a lower quality design (Cuijpers et al. 2010).

Self-help
Different approaches to self-help were used long before the development of the Internet-based treatments of today. Although different modes of delivery have been employed, the self-help book is probably the most well-known and such books are mostly based on cognitive behaviour therapy.
The use of these books is often referred to as bibliotherapy. A meta-analysis revealed that bibliotherapy has a significant effect on depression compared to waiting list control and across the six studies examined, the mean effect size was $d=0.82$ (Cuijpers 1997). A more recent meta-analysis of 29 studies estimated the effect size of bibliotherapy for depression to be $d=0.77$ (compared to controls) (Gregory et al. 2004) while another meta-analysis found that the presence of some form of guidance was the strongest predictor of effectiveness in self-help (Gellatly et al. 2007). Individualized feedback, guidance and support can be seen as non-specific factors that can hardly be contained in a self-help text (Richardson et al. 2010) and perhaps this is one reason why the addition of therapist contact has been associated with effectiveness, which will be elaborated further in the following section.

**Computerised CBT for depression**

The idea that a patient can receive treatment for depression by using a computer is older than the Internet. For example, a study comparing therapist delivered cognitive behaviour therapy with computerized CBT (for depression) in the US was published already in 1990 by Selmi and co-workers, who were able to demonstrate large effects on depressive symptoms compared to waiting list control (Selmi et al. 1990). Patients visited the research centre once a week and worked with the treatment material by using a computer at the facility. The researcher helped the participant at the start of each session and then let him/her continue working independently with the computer for the rest of the session. A total of six sessions were completed in six weeks. There were no significant differences between improvements in the group that received therapist delivered CBT and the group receiving computer delivered CBT, but significant differences were found between the two CBT groups and a waiting list control group, and the between groups effect sizes were large (ibid.). A more recent study replicated these findings (Wright et al. 2005), while another study, comparing computerized CBT to treatment as usual (TAU), was conducted by Proudfoot et al. (2004) within primary care in the UK. The intervention was aimed at patients exhibiting symptoms of depression and anxiety, and a nurse helped the patients for five minutes at the start and end of each session. This computerized intervention was significantly more effective than TAU in reducing depressive symptoms (between groups effect size $d=.47$). Computerized CBT has also been compared with face-to-face CBT in a study with a sample suffering from comorbid depression and problematic drug use, and the two interventions
seemed equally effective although the computerized treatment required only a fifth of the therapist time (Kay-Lambkin et al. 2009).

**Internet-based CBT for depression without guidance**

With the advent of the Internet, the possibilities of treatment by means of computers were increased. First and foremost, treatment became more geographically flexible because there was no longer a need to show up at a certain place and time. Written communication (e-mail) with a therapist became possible, and patients can now complete questionnaires about symptoms directly on the screen and scores are instantly available to the therapist. Another advantage of a web page is that it is very easy to update the content compared to, for example, a CD-ROM with a computer program. Taken together, the above-mentioned advantages make the dissemination of Internet-based treatment much more feasible compared to computerized treatment. The new possibilities has brought new ethical and legal considerations (Dever Fitzgerald et al. 2010) as well as a need for guidelines on how to conduct and report research in the field (Proudfoot et al. 2011). Also, positive and negative expectations of patients about Internet-based treatment arose. In a qualitative study, Bettie et al. (2009) interviewed 24 patients who entered online CBT in southwest England and found that before the online sessions some looked forward to the relative anonymity vis-à-vis the therapist and felt that they could reveal more to someone online compared to in face-to-face contact. Others speculated that the relationship would be more impersonal or mechanic and thought it would make them less inclined to disclose. However, after receiving online CBT, many patients stated that the quality of the relationship with their therapist had exceeded their expectations, and some said that communicating in written form worked well after initial discomfort. Some patients withdrew from online CBT and expressed a strong preference for face-to-face contact. Others thought that their relationship with their therapist developed over time and eventually felt like a “face-to-face” relationship, and several reported that disclosure had been easier due to the online format. It is of course difficult to generalize the findings from a qualitative study, but it seems clear that some patients prefer other forms of delivery, while others find this method acceptable or superior. The same could probably be said about all depression treatments, and the study by Bettie et al. demonstrates that Internet-based CBT can become one (rather than the only) treatment of depression. This view is in line with the results of a survey showing that although face-to-face treatment was the most desired form, about 50% of the respondents expressed an interest in treatment delivered via the Internet (Mohr et al. 2010b).
One of the earliest trials on Internet-based CBT for depressive symptoms was a study by Clarke et al. (2002), in which persons with rather severe symptoms were randomised to having access to a website containing CBT material or to a control condition. The material was divided into seven chapters and mainly focused on cognitive restructuring. The participants in the intervention group had free access to the website and could work with the material at their own pace. No reminders or feedback from clinicians were given. The participants were followed up for 32 weeks and results showed no differences between the intervention group and the control group. The participants logged on to the website on average 2.6 times, which suggests a low level of usage of the intervention material.

In the next study by the same research group, the 169 participants received reminders by postcard or telephone to increase usage of the intervention and hence try to make it effective in reducing depressive symptoms (Clarke et al. 2005). They did not, however, receive guidance or feedback from a clinician. The results showed a significant difference between the control group and the participants using the intervention material and received reminders to do so. The between groups effect size, however, was small (d=.28).

In a third study by this research group, young adults were randomized to treatment as usual or to the Internet-based intervention with postcard reminders (Clarke et al. 2009). After 32 weeks, they found a small but significant effect (d=.20) between the two study conditions. Interestingly, among the female participants the between groups effect size was d=.42.

In another early trial on Internet-based CBT for depressive symptoms (Christensen et al. 2004), the 525 participants were randomised to either Internet-based CBT, Internet-based information or to a control condition. No guidance or feedback from a clinician was received in any of the groups. They did receive information on how to use the website by means of telephone calls from a layperson. The authors demonstrated significant differences between the CBT group and the control group and found a between groups effect size of d=.40 at post treatment. However, they found no difference between those who participated in the CBT group and those who received the information material, as both had a between groups effect size of d=.40 compared to the controls. Later, the same research group reported data from a twelve month follow up of the same sample and there were still significant differences between the two intervention
arms compared to controls, but the effect sizes had been reduced to just below d=.30 in both groups (Mackinnon et al. 2008).

Although little attention has been devoted to the question of which components actually make the CBT-material effective in reducing depressive symptoms in Internet interventions, Christensen et al. (2006) conducted a trial comparing six different versions of their Internet-based intervention. It seemed that an introduction of the core concepts of CBT and feedback after measuring depressive symptoms were not sufficient to reduce symptoms. The problem-solving and stress management modules were not involved in the symptom reduction, but the cognitive restructuring and behavioural activation modules were. Interestingly, none of the versions had an effect size above d=.40 (compared to only introduction of core CBT concepts), and the authors concluded that some kind of support would be required to achieve a stronger effect.

de Graf et al. (2009a) compared treatment as usual (TAU) with an Internet-based intervention without any support from a clinician, and also included, as a third condition, the combination of TAU and the Internet intervention. Adults with depression were recruited from the general population in a large-scale screening in the Netherlands. No significant difference in outcome was found between the three conditions. This means that adding their intervention to TAU did not add to the effect, and the authors speculated that poor adherence to treatment was responsible for the lack of effect and that adding support from a clinician might increase adherence and hence the effect on depressive symptoms. They also speculate that another reason for not achieving the hypothesised effect, was that the participants had higher levels of depressive symptoms compared to other studies in which the same intervention was found to be effective (Spek et al. 2007b). However, this idea is contradicted by the fact that in other studies, high scores at baseline was a predictor of greater effect (Clarke et al. 2009; Kessler et al. 2009). To gain more knowledge about what moderated the effect of this intervention, they published results from a regression model and found that the only two significant predictors of better long-term outcome in patients suffering from depressive symptoms were the amount of homework completed and the expectancy of the patient at the beginning of treatment. Short-term outcome was more favourable in persons who spent more time working with the material and who more frequently logged on to the web site (de Graaf et al. 2009b). A number of participants were later interviewed about their experiences of Internet-based CBT and many suggested that some form of personal...
support should be added in order to help in creating better discipline to work with the material, to have more personal contact and also to be able to go more in depth with the treatment through personal support (Gerhards et al. 2011).

Meyer et al. (2009) compared nine weeks of Internet-based CBT + TAU with TAU, in a sample of 310 participants recruited on depression related Internet forums. No guidance from a clinician was offered and a between groups effect size of $d=.30$ was reported using last observation carried forward. There was a clear dose-response connection, and among the small percentage ($n=10$) of participants that completed all the modules in the study, the effect size was actually $d=1.12$, thus the high attrition rate (45%) was a contributing factor for the low overall effect.

In contrast, Spek et al. (2007b) found no dose-response relationship for their Internet intervention for depressive symptoms, which is interesting because they also had a large drop-out rate, i.e. about 50% completed the Internet treatment. Their randomised trial compared group CBT, Internet-based CBT and a waiting list control group, but did not find any significant difference between the outcomes in the two active treatment groups, although the completion rate was dramatically higher in the group treatment condition (95%). The authors argue that there were more social pressure to complete all the components of the group treatment compared to the Internet intervention and that those who dropped out from Internet treatment did so because they felt no further need. This reason has been suggested for ending treatment without finishing every possible part of it in other studies as well (Christensen et al. 2009) and high symptom severity at intake seems to be the best predictor of treatment completion (Melville et al. 2010), thus dropping out should not be seen as something negative per se. The study by Spek et al. only included persons aged between 50-75 years of age with subclinical symptoms of depression and no clinician support was provided. The between groups effect size was $d=.55$ between the outcomes in the Internet group and the waiting list, and this difference was still apparent at the one year follow up ($d=.53$) (Spek et al. 2008a). Another interesting publication emanating from the same project contains calculations about what type of patient characteristics that predict a favourable outcome in Internet-based CBT (Spek et al. 2008b), a highly relevant issue that has attracted surprisingly limited attention. The result was that higher baseline depressive symptoms, female gender and lower neuroticism scores predicted better outcome. Interestingly, this difference in outcome between genders is also suggested by the results of the
previously mentioned study by Clarke et al. (2009). Another study (Andersson et al. 2004) demonstrated that patients with more previous episodes of depression benefit less from Internet-based CBT and, although significant, the association was weak.

**Guided Internet-based CBT for depression**

Study I in this thesis was the first study to include therapist contact via e-mail together with Internet-based CBT for depression. It was soon followed by several studies using the same strategy – now often referred to as clinician assisted or guided Internet-based CBT. Study I will be described in more detail in the Empirical studies section.

In a three-armed study, Warmerdam et al. (2008) compared the effect of eight weeks of Internet-based CBT, five weeks of Internet-based problem-solving therapy (PST) and a waiting list control group on depressive symptoms. The 263 participants were recruited through advertisements and randomly allocated to the three conditions. The participants received a standardised e-mail at the start of each week containing a lesson with a date specifying when the homework was to be returned to their therapist. Feed-back from the therapist was received within three days and the therapist spent 20 minutes on each patient per week. Both interventions were significantly more effective than waiting list and had similar effect sizes after twelve weeks of follow up (CBT d=.69; PST d=.65). Although clinician support was provided, as well as deadlines, the attrition rate was 45% (similar attrition was found in both intervention groups). In a study by van Straten et al. (2008), Internet-based PST had a medium effect (d=.50) on symptoms of depression and anxiety.

Ruwaard et al. (2009) aimed to provide a great deal of therapist feedback and had a clear structure around this with many templates for different scenarios to be personalized by the therapist. Their intervention was divided into eight treatment phases and the median treatment time was 16 weeks. They found a large between groups effect size of d=.90 between the treatment group and the control group, and the improvements were sustained at the 18 month follow up.

Perini et al. (2009) used an intervention material with both behavioural and cognitive interventions divided into six “online lessons” and advised the participants to complete one lesson every seven to ten days. They had the possibility of e-mail contact with a therapist and were instructed to actively participate in an online discussion group. After eight weeks the
CBT-group had improved significantly more than the control condition and the between groups effect size was $d=0.75$. The therapist spent less than two hours treating each patient.

Many of the above mentioned studies were included in a recent meta-analysis that aimed to summarize the effects of computerized and Internet-based treatments for depression (Andersson & Cuijpers 2009). The analysis comprised twelve studies and made 15 comparisons between a psychological treatment and a control group. Eleven comparisons examined CBT, two evaluated problem-solving therapy (PST) and one psychoeducation. Two studies investigated computerized treatment and ten Internet-based treatment. The result of the meta-analysis was that the overall effect size of computerized and Internet-based treatments for depression was $d=0.41$. However, a clear difference emerged when the authors divided the material into studies with and without support. Studies in which support was provided had a mean effect size of $d=0.61$, compared to $d=0.25$ for studies with no support. This clearly indicates that some form of support or contact is needed to obtain moderate to large effects from these forms of treatment, which is also supported in an earlier meta-analysis on Internet-based CBT (Spek et al. 2007a). A positive correlation between effect size and the amount of therapist support was demonstrated in a review article on Internet-based CBT for depression and anxiety (Palmqvist et al. 2007) and the same was found in a recent review of technology assisted treatment (Newman et al. 2011). In a more recent review of Internet-based psychotherapy for depression it was concluded that large effects are only found in studies with, at the very least, low intensity support, and that completely self-guided interventions are associated with smaller effects (Titov 2011). However, we do not know the critical features of the contact. In a recent trial (Titov et al. 2010a) on Internet-based CBT for depression, the authors compared clinical guidance with guidance that only contained general support and encouragement (without any clinical advice). The participants were randomly allocated to the two forms of guidance/support and both intervention groups worked through the same eight week CBT based intervention. There was no significant difference in outcome between the two groups, indicating that clinical advice may not add anything to support and encouragement without clinical advice. Another recent study showed a large between groups effect size for unassisted bibliotherapy on panic disorder when a clear deadline was given and a structured psychiatric interview was conducted over the telephone (Nordin et al. 2010). This poses questions about the nature of the contact needed in Internet-based psychological
treatment. A related question was elucidated in a study indicating that the individual therapist was relatively unimportant for the effectiveness of Internet-based CBT for the symptoms of depression, but perhaps more important for the secondary outcome measure of quality of life (Almlov et al. 2009).

One recent meta-analysis of Internet-based and computerised treatment only included studies in which the participants had been diagnosed with a disorder, for example, MDD (excluding studies on subclinical problems). The results showed that this form of treatment has medium to large effects on depressive symptoms (Andrews et al. 2010).

Some of the interventions used in guided Internet-based treatment are rather symptom specific, such as modules describing strategies for improving sleep. In many studies, e.g. Study I, modules were given to participants in an inflexible way, possibly making persons who were satisfied with their sleep work with sleep improvement. This led to the idea of tailored Internet-based treatment in which suitable modules are chosen by a clinician before the start of treatment on the basis of the symptoms of the individual patient. It has also been argued that tailoring the content of Internet-based CBT could make it more suitable when comorbidity is present (Andersson 2010). Tailored Internet based CBT has been used successfully in persons suffering from anxiety (Carlbring et al. 2011). This method has been compared with the more established protocol (in which all participants receive all modules) in a trial by Johansson et al. (2010) by randomising participants to tailored Internet-based CBT or to a condition in which all participants received all modules. The effect size of the tailored treatment on depressive symptoms was d=.78 compared to d=.56 for the non-tailored approach. There was no significant difference between the reduction of depressive symptoms in the two conditions.

**E-mail therapy**

While some trials have investigated the possibility of minimizing therapist contact, others have moved in the opposite direction. For example, Vernmark et al. (2010) designed a study to test whether an approach with a high degree of individualised communication, demanding more therapist time compared to guided Internet-based CBT, would lead to a larger effect for Internet-based treatment for depression. In the more individualised condition, a form of e-mail therapy, there was no standardized self-help material, but instead all communication was written for a particular patient and his/her clinical problems. The time spent on each patient was
nearly ten times that spent per patient in the group receiving guided Internet-based CBT, but no significant difference in the effect on depressive symptoms was found. Compared to the waiting list, the effect size for guided Internet-based CBT was d=.56 and for e-mail therapy d=.96. The authors comment that e-mail therapy might not be cost-effective since the time spent on each patient is so high.

The amount and organisation of therapist support differ between studies. In a study by Kessler et al. (2009), therapists and depressed patients had online CBT sessions with written communication, both being online at the same time. Treatment consisted of up to ten of these online appointments of about 55 minutes each. Despite this high amount of therapist time, the effect was d=.81, which is similar to studies of guided interventions with less therapist time. This study thus suggests that there is not much to be gained from a dramatic increase in therapist time, although some form of support seems vital (Andersson & Cuijpers 2009). The ideal amount of therapist time is not known, although in a recent review article supporting the effectiveness of Internet-based CBT for depression and anxiety, the median therapist time per patient was 155 min across the studies (Griffiths et al. 2010), and one to two hours has been sufficient to produce large effect sizes on depressive symptoms in previous studies (Perini et al. 2009; Titov et al. 2010a).

Severely depressed patients are usually excluded from studies on Internet-based CBT (Andersson et al. 2005; Perini et al. 2009) but interestingly enough, they were included and treated in the above-mentioned study by Kessler (2009), where the authors actually found a larger improvement among those with severe symptoms at baseline. Thus we may have to question the notion that this type of treatment is unsuitable for severe depression.

A review of the evidence pertaining to Internet and computerized CBT for depression and anxiety was conducted by the Swedish Council on Health Technology Assessment in 2007 (Statens beredning för medicinsk utvärdering 2007). The report raised an important question about external validity, specifically questioning whether the samples in the studies were representative of public health care patients. After the presentation of that report, the above-mentioned study by Kessler (2009) has however been published, showing significant results in a sample of primary care patients. One study also found that patients from an Internet clinic were largely sociodemographically comparable to those at a standard out-patient clinic,
Although somewhat older individuals and more women attended the Internet clinic (Titov et al. 2010b).

Summary
In summary, there is now substantial evidence that guided Internet-based CBT can be an effective treatment for depression, and its effect size is estimated to be $d=0.61$ compared to waiting list control. The effect has been shown to be maintained until the 18 month follow up. A large proportion of patients suffering from depression find this form of delivery acceptable. It seems clear that some kind of guidance is required to attain moderate to large effect sizes, but little is known about the quantity or quality of the guidance needed for the intervention to be effective. Several trials have indicated that around two hours of therapist guidance are sufficient and that the addition of considerably more time does not produce a commensurate increase in effect. While the strongest support is for the efficacy of treating mild to moderate depression, severe cases have also been treated with success in one study. There are indications that women benefit more from this type of intervention and that patients with greater symptom severity are more likely to finish the treatment and improve more. Positive expectancy and the completion of more homework also seem to predict a higher effect. Studies on samples in clinical settings, and more studies of the long term effects are still required. Tailoring the content of the treatment material to the individual intuitively makes sense but is relatively unexplored. Internet-based CBT for depression has not yet been compared to ADM, nor has combination treatment been investigated by means of a randomised design.

Psychological relapse prevention

Relapse
Many treatments have a documented effect on depression but far from all patients who receive treatment enter remission. In a recent meta-analysis, the mean remission rate after SSRIs was estimated at 42% and after SNRIs at 49% (Machado & Einarson 2010) (remission is typically defined as a score of seven or below on the Hamilton Depression Rating Scale (HDRS) (Hamilton 1960)). Although less than half enter remission as a result of ADM, about 60% respond to it (Cipriani et al. 2009), defined as a 50% symptom reduction. After cognitive behaviour therapy remission rates of 40% (DeRubeis et al. 2005) and 40-45% (depending on symptom severity)
(Dimidjian et al. 2006) has been reported, and the response rate was reported at 56-60% depending on symptom severity (ibid.).

These response and remission rates are not very impressive and unfortunately the prognosis for sustained improvement is also discouraging. Although an isolated episode can often be treated successfully, the risk of another episode within the near future is high (Mueller et al. 1999). This tendency to recur has led to the view of depression as a chronic disorder, and more suitable management models (e.g. involving relapse prevention) have been called for, as it makes no sense to passively wait for the next episode (Andrews 2001). Not only does the time between episodes tend to decrease with increasing number of episodes (Solomon et al. 2000), but the severity also tends to become greater (Kessing 2008), so relapse prevention might actually prevent a deterioration of the illness. The risk of relapse is not the same for all patients, and one of the most well-known risk factors is the presence of residual symptoms after treatment (Judd et al. 1999; McGrath et al. 2006; Paykel et al. 1995). Hence, nearly all attempts at relapse prevention include treatment of residual symptoms. The focus of Study IV in this thesis is the capacity of CBT to prevent relapse in the continuation phase, i.e. when administered after acute phase treatment. The relapse rates related to acute phase CBT fall outside the scope of this thesis.

The concepts of relapse and recurrence are often differentiated (Rush et al. 2006). Relapse is defined as the return of the disorder from a situation of partial remission or close in time after full remission. Recurrence is the return of the disorder after a longer period without symptoms, often referred to as recovery (Frank et al. 1991). However, in this thesis the concept of relapse is used to describe both of the above mentioned situations.

Strategies in psychological relapse prevention
It has been claimed (Nierenberg et al. 2003) that the modern era of relapse prevention for depressed patients started with the report from Frank et al. (1990) investigating the preventive effect of antidepressant medication and interpersonal psychotherapy (IPT) in adult patients suffering from their third (or subsequent) episode of major depressive disorder. The preventive effect of imipramine in the study was considerable, and although the effect of IPT was somewhat more modest, it was found that IPT alone prolonged the time between episodes compared to placebo and thus delayed relapse in the three year follow up.
Well-being therapy (WBT) was designed to prevent relapse in depression and is based on the idea that being well is not identical to the absence of symptoms. Rather, it is argued, well-being comes from, for example, self-acceptance, positive relations with others and autonomy. WBT focuses directly on the episodes of well-being in a patient’s life and explores ways to prolong them, which can include questioning negative thoughts that prematurely interrupt episodes of well-being (Rafanelli et al. 1999). Of special interest in this thesis is relapse prevention based on CBT, which will be described in more detail in the following section.

**CBT-based relapse prevention**

In studies where CBT has been used as an adjunct to other interventions in order to prevent relapse in MDD, it has mainly been aimed at either of two different groups: sufferers from residual symptoms after partial remission or sufferers from recurrent depression currently in remission. These groups can be said to represent two risk factors for relapse. However, they are rarely mutually exclusive and therefore studies often have at least some participants with both risk factors present. This distinction is frequently made in the literature and even if the two groups may not be mutually exclusive, it shows that two different problems are being tackled: relapse after partial non-response and relapse/recurrence after full remission.

A randomised study of CBT based relapse prevention after partial remission from MDD was conducted at a university clinic in Italy by Fava et al. (1994) and included consecutive outpatients with residual symptoms after three to five months of antidepressant medication (ADM). The 40 participants were randomised to ten sessions of individual CBT or ten sessions of clinical management (CM) (including monitoring medication tapering, reviewing clinical status and providing support). All participants tapered off and discontinued ADM and it was demonstrated that the CBT intervention had significantly reduced the residual symptoms at the post treatment measurement compared to CM, after which a follow up phase began. After two years, 15% in the CBT group had relapsed compared to 35% in the CM group, although this difference was not significant (p=.27) (ibid.). After four years 70% in the CM group had relapsed, compared to 35% in the CBT group, which was a significant difference, indicating that CBT for residual symptoms provided after pharmacotherapy has a protective effect (Fava et al. 1996). A later analysis also revealed a tendency towards a protective effect (p=.06) after six years when the relapse rates in the two groups were 50% versus 75% in favour of CBT.
(Fava et al. 1998a). Although limited by the small sample size, this study provided preliminary evidence that CBT might be effective as relapse prevention, and merits further research.

A study with a similar aim was conducted in the UK and included a larger sample (158 participants) with partially remitted MDD after ADM, who were followed for 68 weeks (Paykel et al. 1999). The participants were recruited in psychiatric outpatient clinics and suffered from residual symptoms at randomisation, defined as a score of at least nine on the Beck Depression Inventory (Beck et al. 1961). Participants, all of whom continued their antidepressant medication, were randomised to 16 sessions of CBT or to clinical management, and blinded assessment was conducted to establish relapse (defined as fulfilling MDD criteria for one month). At post treatment there was a trend towards lower levels of depressive symptoms in the CBT group compared to the CM group, but this difference was not significant (p=.07). After 68 weeks, 47% had suffered a relapse in the clinical management group compared to 29% in the CBT group, and this difference was significant. Given the sample size and the blinded assessment, this trial provides more clear evidence that, as an adjunct, CBT can reduce relapse rates among sufferers of residual depressive symptoms. A few years after the aforementioned trial, Paykel et al. decided to conduct a retrospective follow up of the participants, examining the duration of the protective effect of their CBT-intervention. They managed to interview 134 (85%) of the participants from the original trial and found differences between the two groups for up until 3.5 years (although not significant), after which the groups could not be distinguished from each other. It seems that the protective effect of the CBT intervention was strongest at the beginning and then faded. However, it is clear that it had the capacity to postpone relapses (Paykel et al. 2005).

A trial conducted within primary care in Australia randomly allocated GP practices to providing a CBT-based intervention or usual care for depressed patients after the symptom levels had stabilised as a result of initial ADM treatment. Adding this intervention in the continuation phase did not significantly reduce relapse (p=.23) in the sample as a whole (N=110), although patients over 50 years of age exhibited a significant reduction in the number of relapses (Howell et al. 2008).

In addition to the above-mentioned studies aimed at the prevention of relapse in sufferers of residual symptoms, studies have also been conducted to prevent relapse in recurrent depression, where the intervention is
typically administered during a period of remission. One such study by Fava et al. (1998b) used a sequential model in which they first treated consecutive outpatients suffering from recurrent depression by means of ADM, and then randomly allocated the responders to either ten sessions of individual CBT or clinical management (CM). ADM was tapered off and discontinued during the 20-week intervention time during which the CBT group worked with treatment of residual symptoms and relapse prevention. After the conclusion of the intervention, they were reassessed every three months by a clinical psychologist who was blind to the study condition. In the CM group, 80% of the patients suffered a relapse during the two years of follow up, compared to 25% in the CBT group. At a later stage Fava et al. (2004) published results from a six year follow up of the same patients and found that the difference between the CBT and the CM group remained and that at least one relapse had been experienced by 40% in the CBT group compared to 90% in the CM group. This study had limitations, e.g. the sample was small, but the result that 60% of a group with at least three previous episodes of MDD had been relapse free for six years without ADM indicates the clear potential of CBT and definitely merits further research.

Having obtained interesting results in two pilot studies, Jarret et al. (1998) hypothesized that CBT with a continuation phase would result in fewer relapses compared to CBT without such a phase. To investigate this further, they conducted a randomised study with a sample suffering from recurrent depression, in which none of the participants used ADM (Jarrett et al. 2001). They first treated the patients by means of 20 sessions of CBT and then randomised those who responded to either ten sessions of continuation CBT or an evaluation comprising follow up only. After eight months only 10% of the continuation CBT group had suffered a relapse compared to 31% of the control group, and this was a significant difference. The continuation intervention included treatment of residual symptoms, relapse prevention and skills training and was administered as individual face-to-face psychotherapy with an experienced psychotherapist (ibid.).

Mindfulness-based cognitive therapy (MBCT) was designed to reduce the risk of relapse, particularly in sufferers from recurrent depression. The aim of MBCT is partly to treat residual symptoms and partly to teach patients to interpret inner sensations in more adaptive ways (Segal et al. 2001). One of the MBCT trials included patients who had experienced no less than two previous episodes of depression and been successfully treated with
ADM. Results indicated that participants with two previous episodes suffered more relapses after eight weeks of group MBCT compared to the TAU group, although this difference was not significant. In participants with three or more previous episodes, there was a significant reduction in the number of relapses after MBCT compared to TAU (40% vs. 66%) one year after conclusion of group therapy (Teasdale et al. 2000). In a replication, 36% of patients with three or more episodes relapsed after MBCT compared to 78% after TAU, and again there was a non significant increase in the number of relapses in the MBCT group participants with only two previous episodes (Ma & Teasdale 2004). It seems that MBCT can serve as effective relapse prevention in persons with three or more previous episodes. In the third study on MBCT for recurrent depression, participants were randomised to maintaining their ADM or to eight weeks of MBCT plus encouragement to taper off and discontinue their ADM. In the ADM group, 60% had experienced relapse at the 15 month follow up, compared to 47% in the MBCT group (p=.07). The MBCT group had significantly lower levels of residual symptoms at follow up and also experienced higher psychological and physical quality of life compared to the ADM group (Kuyken et al. 2008). Segal et al. (2010) randomised ADM responders to three different conditions in the continuation phase: MBCT, continued ADM or placebo. They found no significant difference in relapse rates between the two active treatments, nor between active treatment and placebo in the sample as a whole. However, for those in unstable remission though, a significant difference was found between active treatment and placebo. In another study, MBCT + TAU increased the time until relapse compared to TAU only, but after 60 weeks of follow up, relapse rates were similar (Bondolfi et al. 2010), which indicates a short term protective effect. A pilot study investigating the effect of MBCT on partially remitted depression had positive results in terms of symptoms but relapse was not measured (Eisendrath et al. 2008).

An ongoing trial on MBCT aims to recruit 375 participants and investigate among other things whether the intervention can decrease suicidality in those who do relapse (Williams et al. 2010).

The finding that the protective effect is only found in persons with several previous episodes, as illustrated in the Teasdale et al. (2000) study, was also evident in a study by Bockting et al. (2005), in which individuals were randomised to TAU and CBT or TAU only after remission from recurrent depression following psychotherapy or ADM. They included persons with at least two previous episodes, but only found a significantly higher
that continued ADM or a dose increase in ADM as well as CBT are among the most effective means of preventing relapse (Hollon et al. 2005; Williams et al. 2009), it appears that CBT did not add any effect to the increased dosage of Fluoxetine (Perlis et al. 2002). Since it is also widely recognized that withdrawal from ADM increases the likelihood of relapse (Hollon et al. 2005; Williams et al. 2009), it appears that continued ADM or a dose increase in ADM as well as CBT are among the most effective means of preventing relapse.

One study revealed that a dose increase in ADM is equally effective in preventing relapse as a dose increase + CBT, indicating that CBT did not add any effect to the increased dosage of Fluoxetine (Perlis et al. 2002). Since it is also widely recognized that withdrawal from ADM increases the likelihood of relapse (Hollon et al. 2005; Williams et al. 2009), it appears that continued ADM or a dose increase in ADM as well as CBT are among the most effective means of preventing relapse.
the alternatives for relapse prevention in MDD. While pharmacological relapse prevention is fairly accessible, CBT in the continuation phase of depression treatment is scarce. Bockting et al. (2010) suggested the use of Internet-based CBT in relapse prevention as one way of improving access for patients.

**CBT-based relapse prevention via the Internet**

An ongoing study is comparing Internet-based CBT to TAU in an attempt to prevent relapse in recurrent depression. However, to date only the trial protocol has been published (Bockting et al. 2011). The participants have a history of at least two episodes of major depression and recovered from the most recent one between two months and two years ago. The intervention is an adapted version of the treatment material used in earlier studies by the same group (Bockting et al. 2005) and participants are asked to rate their mood through text messages (SMS).

A web-based intervention mainly designed for prevention (as opposed to relapse prevention) of depression in persons at risk was tested in a study by Patten (2003), including cognitive restructuring and behavioural activation, although no clinician support was provided. In an RCT they compared the intervention with a web-based program with a similar appearance but only general information about depression. No effect was observed for either of the interventions and no difference in outcome was found between participants who received the CBT material and those only provided with information. The same percentage (12.7%) developed a depressive episode before the three month follow up in both groups. The study had sufficient power (n=764) and a high-risk sample was included, yet the results are in contrast to the positive findings in the above-mentioned meta-analysis (Vittengl et al. 2007) of studies on the prevention of depressive relapse with face-to-face CBT. Given our knowledge of non-guided Internet-based CBT for ongoing depression, it is reasonable to attribute the lack of effect to the absence of guidance.

**Summary**

In summary, CBT-based relapse prevention in partially remitted MDD has been found to be effective up to 68 weeks of follow up, after which the effect disappeared over time. It has also been demonstrated that CBT adds to the preventive effect of continued ADM, but there is also indication that it does not add to the effect of an ADM dose increase. A small study revealed that as relapse prevention for partially remitted MDD, CBT was more effective than discontinued medication after four years. In another
study no significant difference was found compared to TAU from a GP. CBT based relapse prevention for recurrent depression has empirical support when administered to patients currently in remission, especially those with several previous episodes. CBT in the continuation phase has been studied in a meta-analysis and found to reduce the relapse rate from approximately 60% to about 40% within two years. Although these results are promising, CBT interventions in the continuation phase are available to few patients. If provided via the Internet, CBT interventions could be accessed by a larger number of patients. One previous study has investigated the prevention of depressive symptoms via the Internet, but no therapist contact was provided and it was found to be ineffective. The author is not aware of any previous study that has investigated guided Internet-based CBT as a form of relapse prevention in partially remitted MDD.

Self-report of depressive symptoms

Measurement of severity
When a clinician diagnoses a patient with major depression according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association 2000) the severity is typically specified using the levels mild, moderate and severe (with or without psychotic symptoms). The levels are defined by the number of symptoms reported in addition to those required for the diagnosis.

Self-report
Many symptoms of depression are only directly observable by the patients themselves, and self-report is thus the most direct way to measure them. When patients rate their own symptoms using a self-report measure, the purpose is usually not to compare them against diagnostic criteria, but rather to make an inventory of symptoms and grade their severity, presented as a total score. Defined cut-off scores indicating the level of severity have been developed for some self-report measures, and these are frequently used in research to help select certain cases to obtain a sample from the population of interest.

Self-report measures are also used in clinical contexts for the measurement of severity on admission, to monitor change during treatment or as a tool for follow up. Frequently, the use of self-report measures is endorsed in
practice guidelines, for example Practice guidelines Depression, third edition, published by the American Psychiatric Association (2010) and the Swedish national guidelines for the treatment of depression and anxiety disorders from The National Board of Health and Welfare (Socialstyrelsen 2010), and models for measurement based care have been proposed (Trivedi & Daly 2007).

In an empirical study of the perceived usefulness of self-report the researchers introduced self-report measures of depressive symptoms as a standard clinical tool in psychiatric clinics (Duffy et al. 2008). After a year, psychiatrists rated the perceived usefulness of the self-report measure for different purposes during contact with depressed patients. Results showed that self-report measures were helpful in making treatment decisions in 97% of visits. Ninety-four percent of the psychiatrists rated self-report measures as helpful in measuring severity and all of them considered it helpful in monitoring response. Although the psychiatrists in the above-mentioned study found self-report measures helpful, there is some evidence that they do not influence primary outcome in depression or anxiety. A review of nine studies concluded that when self-report was used, clinicians in non-psychiatric settings did not recognize a greater number of cases, nor did they perform more effective treatment (Gilbody et al. 2001). It has also been argued that self-reported outcome is often biased and therefore not worth collecting (Bilsker & Goldner 2002). However, some advantages have also been mentioned, such as the ability to prioritize among patients and assign the right case to the most appropriate staff member (Callaly et al. 2003). The routine documentation of self-reported symptom levels can be a future source of data of effectiveness, complementing our knowledge about treatments from efficacy trials (ibid.). Self-reported symptom levels could also be a complementary source of information in clinical work, which could support or contradict clinical observation, thus obliging clinicians to refine their conceptualization (Trauer 2003) and change the treatment plan when no improvement is observed (Slade 2002). One study has found that the number of in-patient days could be reduced by the use of self-report measures without influencing treatment outcome (Slade et al. 2006).

The results of a survey of psychiatrists in the UK indicate that only 10.5% routinely use self-report measurements to identify cases and measure the severity of depression or anxiety. More than half stated that they never used them for measuring severity, and nearly 60% reported never using them to monitor clinical change over time (Gilbody et al. 2002).
stated that they would be time consuming to use, which has also been indicated in a study on implementation in Australia (Meehan et al. 2006) and that there were insufficient resources for routine use of self-report measures. Another frequent comment from the psychiatrists was that a robust infrastructure to support the process was missing, which was a barrier to the use of self-report and that some form of information technology solution could facilitate its application (Gilbody et al. 2002). It seems that self-report measures would be more widely accepted among clinicians if they were easier to use, and one way of accomplishing this is the introduction of Internet-based questionnaires.

**Internet-based self-report**

Compared to traditional paper and pencil questionnaires, Internet-based ones offer many advantages such as geographic flexibility, since they can be completed anywhere and still reach the clinician immediately. Internet-based self-report measures can be programmed to calculate scores automatically and correctly and store them in a practical way that allows clinicians easy access to them. They can also be programmed to calculate subscales scores, create feedback reports and send these to a clinician and/or the respondent when appropriate. Self-report via the Internet has greater scalability, since the cost of added volume is minor and due to elimination of the process of printing and distribution, Internet-based questionnaires are easier to update. The simplified distribution in combination with scalability has been put forward as an argument for the cost effectiveness of Internet-based self-reports (Naglieri et al. 2004). Other possibilities offered by Internet-based self-report are tailoring the questionnaires to the respondent by skipping irrelevant items and making it mandatory to complete all items before submission (Andersson et al. 2008) and eliminating the risk of ambiguous answers such as ticking between two options. Furthermore, Internet-based self-report measures make it possible to know when the respondent actually answered the questions, which can be difficult when paper versions are used (Tiplady 2010).

Some respondents may also prefer answering questionnaires on the Internet rather than on paper, which was the case in a study of mental health questionnaires (Wijndaele et al. 2007). Another study reported that fewer reminders had to be sent to participants who used the Internet to respond to questionnaires compared to those who answered the same questions on paper and that the Internet group had a slightly higher response rate (Ritter et al. 2004). A randomized comparison showed higher response rates and
fewer missed items in Internet-based compared to paper questionnaires (Kongsved et al. 2007).

One disadvantage of Internet-based self-report measures (and other uses of the Internet) is that not everyone has access. Nevertheless, Internet-based self-report measures can serve as a complement to rather than a replacement of traditional paper questionnaires, at least for as long as some people do not have Internet access. However, in 2009 over 70% of the population of Germany, Australia, the United States and the United Kingdom had Internet access, while the figure for Norway and the Netherlands was over 90% (van Gelder et al. 2010). In Sweden, 90% of the population had Internet access in 2010, and between 2009 and 2010 the percentage had increased in all age groups (Findahl 2010). The increase in Internet use has been rapid and 66% of the Swedish population now uses the Internet on a daily basis, compared to 25% in 2003. Two out of three Swedish users look for health information on the Internet and most of them use search engines for this purpose (ibid.). Since access is high and has grown in most developed countries, non-access might be a temporary problem (van Gelder et al. 2010).

Many studies on Internet-based cognitive behaviour therapy use Internet-based self-report measures of depressive (and other) symptoms, e.g. Studies I and IV in this thesis. This makes the treatment and self-report of symptoms geographically flexible and no papers or letters are required at any stage of treatment. Questions from self-report measures originally developed as paper questionnaires have in many cases been used online without exploring the psychometric properties of the online versions. It is obvious that Internet-based treatment and Internet-based self-report is an attractive combination offering advantages in terms of effectiveness and simplicity to clinicians and patients. However, it has been argued that one cannot take for granted that when a question is answered on the Internet it will produce the same result as when answered on paper (Buchanan 2003; Naglieri et al. 2004), and some differences have been found (Austin et al. 2006). However, it has also been argued that since some previous research has shown that translating a self-report measure for computer use does not necessarily change its psychometric properties, it might be less important to investigate equivalence when established questionnaires are transferred to online use (Epstein & Klinkenberg 2001).

One reason put forward for possible differences between Internet and paper questionnaires is that the computer format changes the way in which
the items are presented. An example is that due to space constraints, the items are typically presented one at a time when answered by computer, rather than as multiple items on a page which is typical when paper and pencil are used (Gwaltney et al. 2008).

Other reasons for a possible difference are changes in respondent behaviour, such as being more (or less) inclined to disclose when answering by computer, arising from a feeling of increased anonymity or social disinhibition (Gwaltney et al. 2008; Joinson 1999). However, behaviour change could also arise from difficulties interacting with the computer, which is often referred to as computer aversion or computer anxiety in the literature (Tseng et al. 1998). There have been indications that this could play a role in the self-report of symptoms because working with the computer per se could result in the symptoms being measured (ibid.). Other results, however, show that this is mainly a problem for people with limited computer experience (Tekinarslan 2008) and that it may decrease as computer use increases.

In a review of the literature by Schulenberg & Yutrzenka (1999), computerized versions of measures of negative affect were compared to the original paper versions. Although they were mostly equivalent, some small differences were found and the authors suggest that lack of computer experience might be an explanation.

The equality of Internet versions of established questionnaires and their paper “ancestors” was investigated in a meta-analysis by Gwaltney et al. (2008), synthesizing the results of 46 studies (often comparing many self-report measures per study). Two hundred and thirty-three differences in mean scores were used to calculate a mean difference percentage between paper and Internet versions of various measures. A mean of the absolute differences was calculated to ensure that positive and negative differences did not cancel each other out. The average absolute difference in mean scores was 2% and there was no statistically significant difference. There was no significant association between computer experience and mean difference, nor a significant association between age and the mean difference. A weighted mean correlation between the Internet and the paper-generated scores was also calculated, using 207 correlations from 32 studies (studies with a larger sample size were given greater weight). The weighted summary correlation was 0.90 and the 95% confidence interval was 0.87-0.92. As the age of the respondent increased, the correlation decreased, although this trend was small. Computer experience was not
related to the Internet-paper correlation. The authors point out that the correlation between scores generated from an Internet version and a paper version should always be placed within the context of the paper-paper test-retest correlation and should ideally closely resemble it. Four studies in the meta-analysis compared the paper-paper correlation (0.91, 95% CI 0.86-0.94) with the paper-Internet correlation (0.88, 95% CI 0.85-0.91) and the authors concluded that they were very similar (Gwaltney et al. 2008).

One important point made in the article is that migrating a questionnaire to Internet use always changes the presentation of the items to some degree and that the extent to which a questionnaire is altered when transferred may per se create differences in the results. The authors concluded that such alterations are not always described in detail in publications, although in the studies included in the meta-analysis they found no indication of more substantial changes and that in most cases “faithful migrations” had taken place. The results of the meta-analysis have to be interpreted with this in mind. The authors of the meta-analysis concluded that further studies of paper-Internet equivalence are unnecessary as long as only minor changes are made during the migration (Gwaltney et al. 2008), which was later elaborated on in the recommendations from the International Society for Pharmaeconomics and Outcomes Research (ISPOR) about the evidence required to support equivalence between electronic and paper based outcome measures (Coons et al. 2009). In these recommendations it is clearly stated that the magnitude of the changes made during the migration process (e.g. from paper to Internet) should determine the amount of evidence needed to demonstrate equivalence. After minor modifications it can be sufficient to interview a handful of respondents about how they perceive the questions. It is not until moderate modifications are made that the authors recommend equivalence testing and in such cases suggest a randomised cross-over design. If substantial modifications are made, they recommend full psychometric testing and that the questionnaire should be treated/tested as a new test. Examples of moderate modifications are a significant reduction of the font size or changing the order of the items, while a substantial modification would involve removing items or changing the recall period. The modifications to the BDI-II and the MADRS-S during the migration from paper to the Internet versions used in Studies II and III can be considered moderate when compared to the ISPOR definitions (Coons et al. 2009).

The International Test Commission (ITC) has also published guidelines on good practice in computer and Internet-based testing and this document
contains recommendations about how to adapt a test originally developed as a paper-and-pencil questionnaire to Internet administration. The ITC recommends showing equivalence in each test separately and, according to the guidelines, it is important to show evidence that the two versions produce similar means and standard deviations and correlate with each other at the expected level derived from reliability estimates. The two versions should also have similar reliabilities (The International Test Commission 2006).

The computerized version of the BDI (first edition) has undergone psychometric testing with a sample of 330 psychiatric in-patients who suffered from moderate levels of depression. Although internal consistency was comparable with that of the paper version, no direct comparison was possible as the study sample did not complete the paper version (Steer et al. 1994). Direct comparisons with the original paper version have been made in other studies, two demonstrating equivalence (Lukin et al. 1985; Peterson et al. 1996) while one showed a difference between the computerized and the paper versions (George et al. 1992). One study also revealed computer-paper equivalence for the BDI-II (Schulenber & Yutrzenka 2001). However, the samples mainly consisted of college students and had low scores, indicating only minimal or mild depressive symptoms. The ISPOR recommends that equivalence trials should be carried out using samples representative of the intended population (Coons et al. 2009). The test conditions are not always the same in computer based and Internet-based self-report. Studies on computer-based self-report measures are typically conducted in a research environment such as a room with several computers. As it is geographically flexible, Internet-based self-report is conducted in many places and the researcher is usually not aware of the exact location of the participants, thus conditions may differ between them.

In one Internet-based study, the MADRS-S and BDI-II were compared using a randomised counter balanced design in which all participants completed all versions. Over 300 participants were recruited via the Internet after a newspaper article was published about an Internet-based CBT trial for panic disorder, hence the sample was self-recruited and mainly suffered from anxiety (Carlbring et al. 2007). Their level of depressive symptoms was mild and reliabilities for both BDI-II and MADRS-S were unaffected by the administration format. The correlations between the paper- and the Internet generated scores were also high (above 0.9). In the case of the MADRS-S, no statistically significant differences
were found between administration formats, but for the BDI-II a main effect was found, showing a higher score for the Internet version. Although statistically significant, the difference was small and of limited clinical importance.

The Internet-based MADRS-S has also been compared to its paper version in a sample primarily suffering from social anxiety and exhibiting mild depressive symptoms. One group completed the Internet version and the other the paper version. The internal consistency was similar in the two versions and there was no significant difference between the mean scores (Hedman et al. 2010).

**Summary**

In summary, clinicians typically find self-report measures valuable when they use them, but according to a survey they rarely do. A common reason is the lack of a robust infrastructure. Internet-based self-report could be an attractive complement that offers many advantages. Internet-based self-report measures have been used in trials on Internet-based CBT but the psychometric properties have not been thoroughly investigated. A large meta-analysis comparing Internet and paper versions of the same self-report measures found no significant differences. Nevertheless, the authors of the meta-analysis recommend psychometric comparison if moderate changes were made during the adaptation for online use. The International Test Commission recommends that every self-report measure should be tested separately. Previous results on Internet-based versions of the BDI-II and MADRS-S have mostly indicated equivalence with paper versions, which is promising. However, these studies have used samples with anxiety as the primary psychiatric complaint and only mild levels of comorbid depressive symptoms. The author is not aware of any previous study on the equivalence of Internet-based and paper versions of the BDI-II and MADRS-S, that employed a sample suffering from moderate to severe depressive symptoms and recruited within health care, nor a sample without pronounced psychiatric problems.

**Beck Depression Inventory – Second Edition (BDI-II)**

BDI-II (Beck et al. 2005) is a self-report measure of depressive symptoms and a revised version of the original BDI (Beck et al. 1961) developed by Aaron Beck and published in 1961. The different forms of the Beck Depression Inventory have been widely used in clinical and research contexts over the years and are available in many languages. BDI-II contains 21 items, each of which consists of four statements, and the
respondents are instructed to choose the statement that best describes their symptoms during the past two weeks. Every item results in a score of 0-3, which produces a total of between 0 and 63 (higher scores indicate more severe depressive symptoms). One major improvement in the BDI-II is that it better captures atypical depressive symptoms compared to its predecessor, as increased appetite and sleep also add to the total score. The psychometric properties of the BDI-II have been found to be good in several publications e.g. the internal consistency has been reported to be $\alpha = 0.94$ in one study (Arnau et al. 2001) and $\alpha = 0.91$ in a study by Beck et al. (1996). According to the manual, the one-week test re-test reliability was 0.93 in a sample of out-patients who completed the original paper version twice (Beck et al. 2005).

**Montgomery-Åsberg Depression Rating Scale – Self rated (MADRS-S)**

MADRS-S was published in 1994 (Svanborg & Asberg 1994) and is the self-rated version of the MADRS that was originally developed as a clinician rated instrument measuring depressive symptoms and published in 1979 (Montgomery & Asberg 1979). The items included in the original MADRS were chosen from a larger set of items on the basis of the magnitude of change during treatment. The items with the highest change scores were chosen to ensure that the scale would be sensitive to change during treatment (ibid.). Nine of the original ten MADRS items were included in the MADRS-S and the new self-rated version was found to have high correlation with the clinician rated version (Svanborg & Asberg 1994). Each item comprises four statements and the respondent is instructed to choose the one that most closely resembles her/his symptoms during the past three days, or the intermediate alternative indicating that she/he has experienced something in-between two statements. A maximum of six on each of the nine items yields a 0-54 score range, with higher scores indicating more severe depressive symptoms. In a psychometric evaluation using a sample of 280 moderately to severely depressed patients, the MADRS-S was found to have satisfactory internal consistency (Cronbach’s $\alpha = 0.84$) and a one-week test-retest reliability (intra class correlation) of 0.78 (Fantino & Moore 2009).
EMPIRICAL STUDIES

Study I

Aims
The primary aim of Study I was to compare the effect of guided Internet-based cognitive behaviour therapy plus participation in an online discussion forum on depressive symptoms with discussion forum participation only. The secondary aim was to compare the effects on anxiety and quality of life in the two conditions.

Methods
Participants were recruited by means of articles in national and local Swedish newspapers and were provided with information about the study and the research group on a webpage. The potential participants could register for the trial directly on the webpage by completing Internet-based self-report measures and answering questions about demographics, computer access and current treatment. They were instructed to complete an online version of the CIDI-SF (Kessler et al. 1998) which gives a probability that the respondent would get a diagnosis had the full CIDI been administered. A probability of 0.55 or higher is the established cut-off for estimating the presence of MDD, which was used as an inclusion criterion. The aim was to include sufferers of mild to moderate depressive symptoms defined as a score of 15-30 on the MADRS-S. Other inclusion criteria were: not suffering from psychosis or bipolar disorder, not started ADM, or changed its dosage, within the last month, never participated in CBT for MDD, completed the pre-treatment measurement and being over 18 years of age. The participants were also required to be prepared to work with the material several hours per week and not have any obstacles to participation (such as upcoming travels). Previous suicide attempts were a reason for exclusion, since it is associated with an elevated risk of future suicide (Hawton et al. 2003). A score of four or higher on MADRS-S item nine led to exclusion to avoid the inclusion of suicidal persons in the study. The use of short self-report measures, with an item measuring how far in the suicidal process the respondent is, has been advocated as a way of assessing suicidality in general and when communicating via the Internet in particular (Bech & Awata 2009).

In addition to the MADRS-S we also used the Beck Depression Inventory (BDI) (Beck et al. 1961), the Beck Anxiety Inventory (BAI) (Beck et al.
and the Quality of Life Inventory (QoLI) (Frisch et al. 1992) as outcome measures.

The participants were randomly allocated either to guided Internet-based CBT and the possibility of participation in an online discussion forum, or to discussion forum participation only. They were randomized by an independent person who drew numbers (each corresponding to a person) from a bowl. The treatment period lasted ten weeks, after which the control group received all the treatment material. All participants were followed up after six months.

The treatment material comprised 89 pages and was divided into five modules, covering an introduction to CBT, behavioural activation, cognitive restructuring, improving sleep and finally the setting of long-term goals. The modules had to be completed in this order and participants did not gain access to the next module until the previous one had been completed. Each participant gave an account of the work completed in the written communication with the therapist, who provided feedback and access to the next module. Messages from participants were answered within 24 hours seven days a week. It was estimated that the therapists spent a total of two hours seven days a week. The conclusion was that guided Internet-based CBT can reduce depressive symptoms in mild to moderate cases. The result was promising and warranted further research on how much therapist contact is required for the treatment to be effective and what components in the material are vital for a positive outcome. The long-term effect of Internet-based CBT was unknown and there was a need to study the effect with a clinical sample.

Results
Of the 117 participants, 85 completed all measurements and were included in all statistical analyses irrespective of the amount of treatment completed. The 32 (27%) persons who withdrew from the trial did not differ significantly in terms of pre-treatment characteristics, and the most common reason for dropping out was that the treatment was perceived as too demanding. Sixty-five percent of the CBT participants completed all modules, and the group completed 3.7 (SD 1.9) modules on average. There were significantly larger improvements in the CBT group compared to the control group for the BDI, MADRS-S and the BAI, but not the QOLI-scores. The between group effect size on the BDI was 0.94 and on the BAI 0.47. We recalculated results for the BDI by replacing missing values with pretreatment scores for drop-outs so that all 117 were included in the analysis. There was still a significant difference between groups, so replacing missing values did not change the result. The correlation between the activity in the discussion forum and the outcome of the participants in the CBT group was not significant. The CBT participants submitted a total of 233 postings in their discussion forum, for the most part about the treatment. In the control group discussion forum, there were 842 postings.
submitted, and they tended to be mainly about the participants’ own problems.

The conclusion was that guided Internet-based CBT can reduce depressive symptoms in mild to moderate cases. The result was promising and warranted further research on how much therapist contact is required for the treatment to be effective and what components in the material are vital for a positive outcome. The long-term effect of Internet-based CBT was unknown and there was a need to study the effect with a clinical sample.

**Studies II & III**

**Aims**

The aims were to test whether Internet-based versions of the BDI-II and MADRS-S were psychometrically equivalent to the original paper versions in a non-depressed sample (Study II) and in a clinical sample with pronounced depressive symptoms (Study III).

**Methods**

The participants in Study II were recruited at a university campus and consisted of students and staff who passed the main entrance. Individuals were approached and asked to consider participating in a research study involving answering questions about mental health on the Internet. While this sample was expected to exhibit few symptoms of depression, the sample required in Study III should present with pronounced depressive symptoms in order for us to be able to answer the research questions. Therefore, the participants were recruited from within psychiatric and primary care in two county councils in Sweden.

The original paper versions of MADRS-S and BDI-II were used and web-pages were designed for administration of the Internet-based versions. The Internet versions had identical wording and all items were included. Although some changes were made in the migration process, the order and font size were the same and it was possible to go back and change answers. The possibility to leave items unanswered was removed for both measures, as the original instruction is to respond to all of them. However, this is a modification, since a possibility to skip items exists de facto in the paper versions, as does the opportunity to choose more than one statement per item, although respondents are requested to chose one statement only in the instructions. When scoring the BDI-II however, the clinician is instructed to only count the answer with the highest score if a respondent
has circled two or more statements in one item. In the Internet versions of both measures used in Studies II and III, the respondent can only choose one statement per item. The items were presented one at a time on the Internet rather than all at once, which is the case in the paper versions. This could be considered moderate modifications according to the ISPOR recommendations (Coons et al. 2009).

Both studies used a randomised cross-over design as recommended by the ISPOR, i.e. all participants completed both versions of the self-report measures but the order was randomised. In Study II, instructions to complete the paper versions first were put into 60 envelopes and instructions for completing the Internet version first were put into the same number of identical envelopes. All envelopes were then shuffled and when a person agreed to participate an envelope was opened. In Study II the first version was completed immediately after recruitment (either on a computer or on paper depending on randomisation), after which the participants received an envelope containing instructions for completing the second version the following day. Although the basic design of Studies II and III was identical, the procedure differed somewhat. In Study III recruitment took place in connection with a randomised trial on Internet-based CBT for ongoing depression, and Internet and paper versions were completed as part of the registration for the treatment trial. As soon as a person provided informed consent for the treatment trial, she/he was randomised to completing the paper or Internet version first by opening one of the numbered envelopes prepared by a statistician using block randomisation. After randomisation, instructions were sent by letter. As soon as the answers to the first version were received, a letter with instructions for the second version was sent out.

Results
The 71 participants in Study II had a mean score of 7.2 on the (paper) MADRS-S, which indicates mild depressive symptoms (just above the cut-off score of seven) and thus very close to the range of symptom free (0-6), while on the (paper) BDI-II they had a mean score of 8.4, which indicates minimal symptoms. In Study III the 87 participants had a mean score of 23.8 on the (paper) MADRS-S, which indicates moderate depressive symptoms, and 30.6 on the (paper) BDI-II, indicating severe symptoms (just above the cut-off score 29) bordering on moderate symptoms.

The correlation between the paper BDI-II and the Internet version was 0.94 in Study II and 0.89 in Study III, which should be compared to the test-
retest correlation of 0.93 in the manual (paper-paper). The correlation between the paper MADRS-S and the Internet version was 0.92 in Study II and 0.84 in Study III.

The internal consistency of the MADRS-S was very similar in the paper ($\alpha=0.91$) and Internet ($\alpha=0.90$) versions in Study II, as well as in Study III, where the Internet version produced alpha levels of $\alpha=0.73$ (Internet first group), and $\alpha=0.81$ (paper first group) and $\alpha=0.81$ for the paper version in both groups.

The internal consistency of the BDI-II was very similar in the paper ($\alpha=0.94$) and Internet ($\alpha=0.95$) versions in Study II. In Study III the internal consistency in the Internet-version was $\alpha=0.87$ (Internet first group) and $\alpha=0.89$. For the paper version it was $\alpha=0.89$ (Internet first group) and $\alpha=0.90$ (paper first group).

When comparing the mean scores of the two versions in the two groups 2×2 ANOVAs were used. In the case of the MADRS-S there was no main effect for version (Internet or paper) in either of the studies. Nor was there any significant effect for version for the full BDI-II in either of the studies, although in the case of item nine (questions about suicidality) there was a significantly lower score for the Internet-version in Study III. The between groups effect size was $d=0.14$.

In Study II no main effects were found for order and no interaction effects for either of the measures. In Study III however, there were significant main effects for order for both measures, as well as significant interaction effects. The main effects for order can be interpreted as a true difference in the levels of depressive symptoms in the two groups, or alternatively as a tendency for the order to affect the scores so that completing the paper version first and the Internet version second would consistently produce higher scores compared to the reverse order. The interaction effects between order and version found in Study III mean that the order of administration affects the difference between the first and second measurement if different versions are used.

The conclusion of Studies II and III was that the MADRS-S can be transferred to online use without affecting the psychometric properties, as long as the versions are not switched during repeated measures. The properties of the BDI-II were mostly unchanged after the migration, although a small but significant difference occurred in the question about
suicidality. This requires further investigation since an underestimation of suicidality could have serious consequences.

**Study IV**

**Aims**
The aim of study IV was to investigate whether participation in guided Internet-based CBT after other treatment led to fewer relapses into major depression compared to participation in a control condition for sufferers of partially remitted MDD.

**Methods**
Participants should not fulfill the criteria for MDD at recruitment, but should have done so at least once during the previous five years. They should be at least 18 years of age and suffer from mild residual depressive symptoms defined as a score of no less than seven and no higher than 19 on the MADRS-S. Any medication should have been stable for one month and any psychotherapy should have ended 30 days before recruitment. Another inclusion criterion was past treatment for MDD, either pharmacological or psychological (by a licensed psychotherapist or psychologist). Fluency in the Swedish language was required as well as Internet access. Exclusion criteria were having an addiction problem, psychosis or bipolar disorder, or being suicidal defined as a score higher than four on the MADRS-S item nine. The participants were recruited by means of advertisements in Swedish newspapers and potential participants could read about the project and research group on a website, from which they could also print out the consent form.

The recruitment process started with self-report via the Internet, and those who fulfilled the inclusion criteria in this step were interviewed by telephone with the questions about depression from the Structured Clinical Interview for DSM-IV axis I Disorders (SCID-I) (First et al. 1998) and some questions about previous treatment and the use of alcohol and illegal drugs. The final decision about inclusion was made at a diagnostic conference with a psychiatrist and a psychologist present. The 84 participants were then randomised into two groups by drawing numbers from an opaque bowl.

Randomisation was followed by a ten week treatment period during which the participants in the CBT group worked with the treatment material, which was divided into modules and sent to them one at a time. Only after
completion of one module did they receive the next one from their personal therapist, who also provided feedback on completed work. The modules covered nine themes such as behavioural activation, cognitive restructuring and physical activity, each of which included an obligatory basic module that had to be completed in a fixed order. After finishing the basic module, the participant could choose to work with a more advanced module on the same theme, or move on to the next basic module on the next theme.

Participants in both groups had the possibility of e-mail contact with the study staff during the whole study and the contact was asynchronous. Responses were typically sent within 24 hours on working days. Every month participants in both groups completed the MADRS-S online to monitor depressive symptoms in general and suicidality in particular. After the ten-week treatment period and after six months the participants completed the MADRS-S, the BDI-II as well as the Beck Anxiety Inventory and WHOQOL-BREF (Skevington et al. 2004) (a self report measure of quality of life).

Relapse was defined as fulfilling the DSM-IV criteria for MDD at any point after the start of the study and was established in a telephone interview. All participants who scored over 19 on the MADRS-S in one of the monthly ratings were interviewed. All participants were interviewed, irrespective of MADRS-S score, after the ten week treatment period and after six months.

Results
At the six month follow-up, complete data were obtained from 71 participants, which means that the study had an attrition rate of 15.5%. Those who provided incomplete data did not differ from the other participants in terms of age, gender, symptom severity at baseline, previous pharmacotherapy, number of previous episodes, educational level or the proportion of relapses. However, a higher proportion of the drop-outs had a history of psychotherapy.

On average, 6.3 basic and 1.7 advanced modules were completed and a mean of 11.5 messages sent from a CBT participant to her/his therapist while a mean of 15.3 messages were sent from a therapist to a CBT participant. It is estimated that 2.5 hours of therapist time was spent per CBT group participant.
A log rank test revealed that significantly fewer participants in the CBT group (10.5%) suffered a relapse compared to those in the control group (37.8%) ($\chi^2=7.451$, $p=0.006$), before the 6 month follow up. A non-significant trend ($p=0.051$) was found towards a larger reduction in residual symptoms in the CBT group. A Cox regression showed an association between reduction of residual symptoms (from pre to post treatment measurement) and the risk of relapse in the sample as a whole ($p=0.003$, hazard ratio=0.914). This means that a five-point improvement on the MADRS-S reduces the risk of relapse by approximately 36.2% (in the full sample). The between groups effect size from pre- to post treatment measurement was $d=0.33$ (MADRS-S). There was a non-significant trend towards a higher remission rate in the CBT group after six months when measured by the MADRS-S ($p=0.06$) but not when measured by the BDI ($p=0.89$).

The conclusion of Study IV is that Internet-based CBT can reduce the relapse rate in persons with partially remitted depression. Symptom reduction is likely to contribute to the preventive effect. However, as no significant reduction was found, the extent to which the intervention was able to reduce symptoms remains unclear. The results warrant further research to investigate the possibilities and limitations of Internet-based relapse prevention.

**Ethical considerations**

Participation in the studies in this thesis was voluntary and based on informed consent, and we received approval from the Ethical Review Board in Uppsala. All information about individuals was kept confidential and data was published in such a way that no single participant can be identified. All participants were informed of their right to end participation at any time without giving a reason. We did not try to influence the participants to refrain from, end or postpone participation in other treatments or examinations during the studies.

In the treatment studies (I and IV) the main ethical considerations concerned the use of a control condition and handling the risk of suicide among the participants. In Study I, the control condition can be described as a delayed treatment condition since the participants received exactly the same treatment material as the intervention group but ten weeks later. This was considered ethically justifiable as the participants gained access to treatment that was hypothesised to be effective. In study IV the control
condition did not receive treatment, but the participants could contact a therapist by e-mail and completed monthly self-ratings of symptoms that were monitored by a psychologist and feedback on these ratings was provided. The main benefit of participation for the controls was probably that relapses were detected and treatment options discussed with a therapist. Despite the fact that no treatment for the controls was provided, we considered that the benefit of participation outweighed the risks. Suicide risk was dealt with in two ways in Studies I and IV. Persons considered as having an elevated risk were excluded before the study start and encouraged to seek treatment in primary or psychiatric care. Suicidality was also rated in every self-report of depressive symptoms and monitored by the therapists in the study.
DISCUSSION

Main findings

In Study I we were able to demonstrate that guided Internet-based cognitive behaviour therapy can reduce depressive symptoms and anxiety in persons suffering from mild to moderate levels of depressive symptoms. The intervention had a large effect on depressive symptoms and improvements were sustained for at least six months. The level of activity in the discussion group was markedly higher in those participants not receiving active treatment.

In Study IV we were able to show that guided Internet-based cognitive behaviour therapy after other treatment can prevent relapse in MDD in persons with partially remitted depression, hence improving their prognosis. In this group with only mild residual symptoms, the treatment had a small effect size on symptoms, but a substantial effect on relapse i.e. a reduction from 37.8% to 10.5%.

It is possible to achieve the above-mentioned effects (Studies I and IV) with approximately 2-2.5 hours of therapist time, used to guide participants through treatment via e-mail.

In Studies II and III we were able to show that Internet-based versions of the MADRS-S and BDI-II (self-report measures of depressive symptoms) have largely the same psychometric properties as the paper-and-pencil originals, both in a sample with minimal depressive symptoms and in one with moderate to high symptom levels. Correlations between the scores produced by the online and paper versions were high and internal consistency was similar. Suicidality was rated significantly lower on the Internet when the BDI-II was used, meaning that there could be a tendency to underestimate the risk of suicide when this measure is used online. The difference, however, was small (d=0.14). Interaction effects were found between order of administration and version, so even if the Internet versions can be used as a complement in clinical work and research, one should always use the same version during repeated measurements.
DISCUSSION

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In Studies II and III we were able to show that Internet-based versions of the MADRS-S and BDI-II (self-report measures of depressive symptoms) have largely the same psychometric properties as the paper-and-pencil originals, both in a sample with minimal depressive symptoms and in one with moderate to high symptom levels. Correlations between the scores produced by the online and paper versions were high and internal consistency was similar. Suicidality was rated significantly lower on the Internet when the BDI-II was used, meaning that there could be a tendency to underestimate the risk of suicide when this measure is used online. The difference, however, was small (d=0.14). Interaction effects were found between order of administration and version, so even if the Internet versions can be used as a complement in clinical work and research, one should always use the same version during repeated measurements.
Methodological considerations

The randomised design in Study I was a strength, however, it was impaired by the cross-over design that made the six month follow-up less informative from a scientific perspective. At the time it was deemed a necessary compromise for ethical reasons. This may have been overly cautious and due to an initially sceptical view of such treatment when the Internet was less established, and in hindsight we could have waited at least six months before administering the treatment to the control group. It is interesting to compare this with Study IV, in which the control group did not receive any treatment, which evoked no criticism or comments from the ethical review board. This cannot be fully explained by their lower symptom levels at intake because they had all suffered previous episodes and our stated intention was to recruit a sample with a high risk of relapse into full symptomatic depression.

In Study I, an Internet-based version of the CIDI-SF was used to establish a likely diagnosis of depression, which has been shown to have fairly low concordance with a clinical interview (Carlbring et al. 2002). We should therefore have used a clinical interview to obtain a better informed perception of the clinical features of our sample. The design used in Study I makes it possible that people without major depression were included.

In Study I the definition of mild to moderate depressive symptoms (a MADRS-S score of 15-30) was perhaps too narrow in range. According to established norms, the upper limit for moderate symptoms is approximately 35 (Snaith et al. 1986). Again, we might have been overly cautious due to ethical considerations.

Since some participants in both groups were receiving antidepressant medication in studies I and IV, we were unable to isolate the effect of Internet-based CBT as a sole intervention. In many participants we studied the effect of adding this intervention to existing ADM.

Both groups in Study I had access to a separate discussion forum. The activity in the forum was higher in the control condition and it cannot be ruled out that it had an impact on the participants. In previous studies however, most of the evidence indicates that participation in such forums has no effect on depressive symptoms (Melling & Houguet-Pincham 2011).
Since we recruited participants through the media in Study I, the representativeness of the sample can be questioned. The educational level of the sample is higher than that of the general Swedish population, so it may not be possible to generalize the results to the population as a whole.

In Studies II and III we used a randomised cross over design that controls for confounding variables such as order effects and differences in depression scores between groups, as recommended by the ISPOR (Coons et al. 2009). However, there is one important psychometric measure that cannot be calculated using this design, namely test-retest reliability, which is a limitation.

Some changes were made to the questionnaires during the migration process from paper to Internet; most importantly the items were presented one at a time, rather than all at once. This has, however, been found to be psychometrically equivalent in an earlier study (Thorndike et al. 2009). The possibility to circle more than one option and skip items was also removed. This may be considered a limitation, since it introduces the possibility that the alterations as opposed to the medium (Internet/paper) are the cause of any differences.

The attrition in Study II is difficult to analyse since the participants were anonymous and we have very little data on them. We have no data on the 33 who failed to return the questionnaires and a minority of the participants did not reveal their gender, so it is possible that those who dropped out differed from the rest of the sample in some respect.

In Studies II and III, all participants agreed to take part in a research study involving use of the Internet and hence might have a positive attitude towards it. This might have resulted in a biased sample. Since the participants in Study II were recruited on a university campus, it is reasonable to assume that they were relatively familiar with computers, perhaps more so than the general population. Therefore, it is difficult to generalize the results to all people with minimal depressive symptoms. In Study III however, recruitment took place within primary and psychiatric care, thus the results can be generalised to this setting.

Social disinhibition and computer anxiety have been suggested as reasons for potential differences between Internet-based and paper-and-pencil versions of questionnaires. These factors were not investigated, which limits the scope of the studies.
In Study IV a randomised design without cross-over was used, which enables meaningful long-term follow-up. Initially we believed there was a risk that more participants in the control group would drop out because of this, but the attrition rates turned out to be similar in both groups.

An obvious limitation in Study IV is the method employed for diagnosing relapse. After each monthly self-rating, participants who scored over 19 on the MADRS-S (moderate symptoms) were interviewed by telephone using the questions pertaining to depression in the SCID-I. However, it is possible to fulfill the diagnostic criteria without scoring over 19 on the MADRS-S, and such cases might have remained unnoticed. Another problem is that not all participants completed the self-rating every month and perhaps some of them would have scored over 19 had they filled them out. This could also lead to unnoticed relapses. To capture such relapses we interviewed all participants post-treatment and at the six month follow-up. Nevertheless, there is still a risk that someone have experienced an undetected episode and spontaneously recovered from it before the next interview. The mean duration of an episode has been estimated at 16 weeks (Kessler et al. 2003), and the longest possible time between interviews in the study was 26 weeks (between post-treatment and the six month follow up) leaving a time window for undetected relapses to enter remission spontaneously. However, this problem exists in both groups, and since there was no difference in the number of completed monthly self-reports between the groups, it is unlikely that it affected the difference in relapse rate between them. Nevertheless, the absolute levels of relapses in both groups might have been underestimated, and a better design would have been monthly interviews with all participants. Face-to-face rather than telephone interviews could also have added clinical information such as posture and facial expressions, although previous results show that clinical interviews over the telephone are valid (Rohde et al. 1997). Independent interviewers who were blind to allocation would have been preferable to minimise the risk of bias. However, none of the participants were interviewed by their own therapists (contact for guidance/support during the intervention phase), and a structured interview was used. We cannot rule out that the interviews per se had an effect on the outcome, and since the control group participants were interviewed on more occasions, it might have affected the results.

In Study IV the aim was to recruit persons who after treatment attained only partial remission and intervene to improve their prognosis. Due to the
design employed, however, it is possible that some patients had been in full remission before acquiring symptoms again and could therefore be characterized as suffering from subsyndromal symptoms following remission. Since we recruited participants by means of newspapers advertisements, one must be careful when generalizing the results. The educational level in the sample was relatively high.

Another limitation of Study IV was the short follow-up time, however, the results of a two year follow up will be presented in a future publication.

A strength is that we included persons with heterogeneous acute phase treatments, which increases external validity because it resembles the diversity in many clinical settings.

**Scientific implications**

Study I was the first study of Internet-based CBT for depression that included guidance from a therapist. The effect size was larger than in earlier studies of non-guided Internet-based CBT, which was probably its main scientific contribution. More recent studies (Perini et al. 2009; Ruwaard et al. 2009), a review (Titov 2011) and a meta-analysis (Andersson & Cuijpers 2009) have confirmed that guidance leads to better outcome than self-guided Internet-based CBT. It also seems that there is little to be gained from increasing the amount of therapist time above 2-2.5 hours. For example, although Ruward et al. (2009) devoted between seven and 14 hours of therapist time to each patient, their treatment did not appear to be more effective than that in Study I. Recent results indicate that we know little about what the guidance/support must contain in order to be effective (Titov et al. 2010a), and surprisingly little attention has been devoted to this question. However, in an interesting pilot study, Mohr et al. (2010a) has developed a theoretical ground for their guidance and this is hopefully the beginning of a close exploration focused on the guidance itself in Internet-based interventions.

Studies with longer follow-up times than in Study I have been published, but we know little about the effects after 18 months, which can be considered a major limitation in our knowledge. Samples recruited in clinical settings are still rare in studies of Internet-based CBT for depression. However, the study by Kessler (2009) was conducted in primary care and had a large effect, but this needs to be replicated and the amount of therapist time was very high. Future studies should investigate
the effects of Internet-based CBT in clinical samples with minimal (e.g. 2h) therapist contact. Large effectiveness trials treating consecutive patients would contribute considerable knowledge to this field. Another limitation is that no studies have compared guided Internet-based CBT for depression with ADM, and more studies are needed that make a comparison between Internet-based and face-to-face CBT for depression.

The most important finding in Study IV was the lower relapse rate in the CBT group compared to the control group and we are not aware of any earlier studies on Internet-based relapse prevention for partially remitted MDD. Previously, traditional face-to-face CBT was found to have this effect in some studies (Fava et al. 1996; Paykel et al. 1999) but showing that these interventions also can prevent relapse when delivered via the Internet is important, as this method of delivery can make it accessible to larger numbers of patients. The finding that relapse in MDD can be prevented by Internet-based CBT has to be replicated, and it is not yet known if it will have the same effect in a clinical sample. It is known from other studies that traditional CBT can also prevent relapse in recurrent depression when administered between episodes (when the syndrome is in full remission) (Fava et al. 2004), but it has not been studied whether Internet-based CBT could be effective in these cases. Knowledge is lacking about which parts of the intervention are essential for the preventive effect or which patients benefit most. In Internet-based CBT for acute depression there is an indication that cognitive restructuring and behavioural activation are the most important interventions (Christensen et al. 2006), however this may not be the case in relapse prevention. Treatment of residual symptoms is always present in relapse prevention but the goal is usually more comprehensive including, for example, teaching mindfulness skills and encouraging physical activity. The fact that we found a clear difference in relapse rates, but not a significant difference in the reduction of residual symptoms, could be due to more preventive strategies being responsible (at least in part) for the prevention of relapse. It is not known what components of the Intervention in Study IV were responsible for preventing relapse and future studies should investigate this in order to optimize the effect.

In Study IV we used a fixed set of basic modules and a fixed order. This might force patients to read irrelevant material, for example about how to improve sleep for patients with no sleep problems. This could decrease motivation, and future studies should investigate the possibility of individually compiled sets of modules, tailored to the clinical picture of
each patient in relapse prevention. Another possibility is to allow the patient some influence over the modules that constitute the treatment material, which has been tested with promising results in anxiety disorders by Andersson et al. (2011).

There are many possibilities when it comes to Internet-based relapse prevention, the most obvious being the use of the method in persons with other mood disorders (Barnes et al. 2007), anxiety or eating disorders. There are possibilities to add this to Internet-based acute phase interventions or to face-to-face interventions such as group CBT for depression, or in-patient care (Ebert et al. 2010).

Studies II and III indicate that Internet-based versions of the BDI-II and MADRS-S are largely psychometrically equivalent to their original paper versions when completed by two samples in which this had not previously been investigated, to our knowledge. Perhaps the most important result is that a moderate to severely depressed sample rated their symptoms at the same level on the Internet as on paper. The test-retest reliability of the Internet-based versions of the MADRS-S and BDI-II is still unknown, and future studies should investigate this. In Study III the participants rated their suicidality somewhat lower on the Internet based BDI-II than in the paper version. If suicidality is underestimated it could have serious consequences and, despite the fact that the effect size was small, this should be investigated further. Our sample had a very low score on suicidality, so we have no data on how suicidal respondents rate their suicidality on the Internet compared to paper. Future studies should use samples with elevated scores on item nine in order to be more relevant.

The results for the full scales are in line with the meta-analysis by Gwaltney et al. (2008) indicating very small differences between Internet and paper versions of questionnaires. They are also in accord with studies on the same questionnaires but with samples primarily suffering from anxiety (Carlbring et al. 2007; Hedman et al. 2010).

Many studies have now tested CBT provided exclusively on the Internet, however hybrid solutions (a mix of face-to-face and Internet sessions) have been suggested (Andersson et al. 2009) and are also being tested (Jacmon et al. 2009). Hybrid solutions have previously shown good results in social phobia (Andersson et al. 2006) and it is reasonable to assume that in some forms of treatment, the Internet will be used alongside face-to-face contact.
Internet-based treatment for depression within an ethnic minority is now being tested in the Netherlands (Unlu et al. 2010), which highlights the fact that it is not yet known how well this form of therapy works in different sub-groups in western society, or other parts of the world. We also have no knowledge of how Internet based treatment works for people with disabilities, and future studies should investigate the suitability of this form of treatment for different groups and sub-groups.

Another development that may change Internet-based treatment is the fact that more and more people access the Internet through their mobile phone. This means that access to treatment material is increased, but it also offers completely new possibilities in treatment such as rating symptoms in almost any moment of the patient’s day-to-day life rather than in a situation when she/he is sitting down in front of the computer. Another possibility is the use of reminders that reach the patient without delay in daily life, which is already in use in a trial by Bockting et al. (2011) on relapse prevention for recurrently depressed persons. The use of mobile phones in psychological treatment has barely started and empirical studies should investigate the possibilities and limitations.

Clinical implications

Overall, this thesis demonstrates that health care providers can use the Internet for self-report, treatment and relapse prevention in many cases of depression. In some cases, this could mean that the Internet is merely employed for one purpose (for example self-report) during their contact with health care professionals, yet for others it could mean that the Internet is used for most purposes. Since this is a more efficient way of working than face-to-face (Bergström et al. 2010), larger numbers can be offered effective interventions. Not only does this mean that more patients can receive treatment or relapse prevention but also that they can work through it at a time and place of their own choice without the need to travel to a clinic, thus saving both time and money. Internet-based treatment is also potentially less stigmatizing compared to visiting a psychiatric clinic.

Study I, as well as later studies on guided Internet-based CBT, show that it can be an effective treatment for depression. Since the treatment can be completed with only two hours of therapist time, it is likely to be cost effective as well, and implementation in public health care would complement available treatments for MDD. Since there is a shortage of
therapists trained in CBT in many places, an Internet-based approach to CBT could be a more effective way of using the available staff, making it possible to treat more patients in the same amount of time. Since not all patients have access to the Internet, and some of those who have will not be interested in this kind of treatment, Internet-based CBT should not be seen as a replacement, but rather as a complement to other treatments.

Although much less is known about Internet-based relapse prevention compared to Internet-based acute phase treatment, the potential use in clinical settings would be considerable if further empirical support emerges in future studies. One possible use can be after partial success with ADM in both primary and psychiatric care. This could be a method of providing psychological relapse prevention for large numbers of patients. An Internet-based intervention, such as that used in Study IV, could also be part of a sequential approach to treatment that has been described by Fava and Tomba (2010) as comprising a sequence of different treatments, performed by a multidisciplinary team. If effective relapse prevention was to reach a large majority of patients with residual symptoms after other treatment, it could potentially reduce the number of depressive episodes for these patients, and thus their consumption of health care in the long term.

Studies II and III in this thesis, together with previous research, support the use of Internet-based self-report of depressive symptoms in clinical settings, both in face-to-face contact with patients and when Internet-based treatments are used. With regard to the BDI-II, one must bear in mind the small reduction in the score on the item measuring suicidality (item nine) observed in study III, although when it comes to the MADRS-S, the suicidality ratings seem to be equivalent in paper and Internet versions. The spread of the use of online solutions for measuring symptom levels could make the employment of self-report more flexible and user-friendly, compared to paper-and-pencil versions. The advantages discussed in the Introduction can probably make Internet-based self-report more attractive to use for both the patient and clinician, and hopefully employed more frequently. However, not all patients have Internet access, and thus Internet-based self-report can become a complement rather than a replacement, although lack of Internet access is a rapidly diminishing problem.

The initial implementation of Internet based treatment, self-report measures and relapse prevention for depression in Sweden will most likely take place in psychiatric and primary care. However, Internet-based
Interventions for depression can also be relevant in other parts of the health care system, exemplified by a trial testing an intervention for depression specially developed for patients with diabetes (van Bastelaar et al. 2011), and an Internet-based intervention for older adults with depression and comorbid cardiovascular disease (Cockayne et al. 2011). Internet-based self-report of depressive symptoms could also be used in many areas of health care, e.g. for mothers postpartum.

Internet-based CBT for ongoing depression is not only evidence based but also recommended in the national guidelines for the treatment of depression and anxiety disorders (Socialstyrelsen 2010). Therefore it should be implemented across the country – not in order to reduce costs, but to enable us to treat more patients.

In summary, it is possible for health care providers to manage many cases of depression via the Internet.
**SAMMANFATTNING PÅ SVENSKA**

**(SUMMARY IN SWEDISH)**

Kognitiv beteendeterapi (KBT) är en effektiv behandling för depression men tillgången är begränsad. Ett sätt att öka tillgången till KBT är att tillhandahålla den via Internet, och i Studie I i denna avhandling testades detta tillsammans med terapeutkontakt via e-post vilket visade sig ha en god effekt på depressiva symtom och ångest. Resultaten har replikerats av forskargrupper i andra länder och det mesta tyder på att någon form av terapeutkontakt krävs för att få en god behandlingseffekt. Det tycks dock inte krävas mer än 2-2,5 timmars arbetstid för en hel behandling.


Prognosen på lång sikt efter att ha tillfrisknat från depression är dålig och återfall är vanligt. Mellan en tredjedel och hälften av alla som blivit bra av medicin eller KBT återfaller inom ett år i en ny depressionsepisod. KBT som är speciellt inriktad på att förhindra återfall har visat sig minska återfallen men eftersom tillgången på KBT-utbildad personal är låg används detta sällan i klinisk praktik. Studie IV designades för att undersöka möjligheterna att tillhandahålla KBT-baserad återfallsprevention via Internet och resultaten visar att färre återfaller efter att ha fått interventioen jämfört med dem som endast gjorde skattnings av sina symtom. Det fanns en tendens till att fler personer hade blivit av med sina restsymtom efter sex månader bland dem som fick interventionen och en minskning i symtomnivå var kopplat till en lägre risk för återfall.
Arbetstiden per patient var 2,5 timmar och metoden kan bli ett effektivt sätt att förhindra återfall hos ett stort antal patienter.

Resultaten i den här avhandlingen tyder på att vårdgivare kan använda Internet i syfte att behandla personer med depression och för att tillhandahålla återfallsprevention samt för att administrera självskattningsformulär som mäter depressiva symtom.
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