Chapter 1

General introduction
Background

Depression is one of the most prevalent mental disorders in the world. Worldwide, around 340 million people are affected by this disorder (Alonso et al., 2004; WHO, 2004). The probability of developing a major depressive disorder during one’s lifetime is 16.6% (Kessler et al., 2005). In the Netherlands, 5.8% of the adult population suffer annually from depression, which is almost equal to 589 thousand people (Bijl et al., 1998). And every year 289 thousand new cases of depression arise in the Dutch adult population (Meijer et al., 2006). When depression is defined as scoring above a cut-off score on self-rating depression scales, prevalence rates are even higher (Beekman et al., 1999). The recurrence rate is high: 83% of those who recovered from a major depression experienced a recurrence within the next five years (Mueller et al., 1999).

At an individual level, depression has considerable impact on peoples’ quality of life (Saarni et al., 2007; Üstün et al., 2004). In the Netherlands, the disability weight of depression is 0.46 which means that 46% of one year spent in depression is regarded as “lost” - almost as if the person was dead. The remaining period is valued as good health (Meijer et al., 2006). Depression is also associated with increased mortality rates; the risk of dying is 1.81 higher than in non-depressed people (Cuijpers and Smit, 2002). Importantly, it was also found that the increased risk not only exists in major depression, but also in subclinical forms of depression. The increased mortality rate for depression is not only related to suicide. Other probable causes include a less healthy life style or comorbid physical disorders.

Depression not only has a severe impact at the individual level, the consequences at the population level are also enormous. Major depression is currently the fourth disorder worldwide in terms of disease burden, after perinatal conditions, lower respiratory conditions and HIV/AIDS. It is expected to be the disorder with the highest disease burden in high-income countries by the year 2030 (Mathers and Loncar, 2006). Depression is responsible for an annual loss of 157,700 disability adjusted life years (DALYs) in the Netherlands (Meijer et al., 2006). Besides, depression is associated with high levels of service use and huge costs (Bijl and Ravelli, 2000; Cuijpers et al., 2007b; Smit et al., 2006a). In 2005 the Netherlands spent 68.5 billion euro on healthcare and related welfare costs of which more than a fifth were spent on mental disorders. Depression is one of the more expensive mental disorders as 1.1% of the total health care costs can be attributed to this disorder (Poos et al., 2008). Due to its high prevalence, heavy disease burden and substantial economic consequences, the treatment of depression is clearly important.

Psychotherapy for depression

The Dutch guidelines for the treatment of depression recommend pharmacotherapy and/or psychotherapy for a depressive disorder that lasts at least three months
If psychotherapy is chosen, then cognitive behavior therapy (CBT), behavior therapy or interpersonal psychotherapy are recommended. CBT is the most widely researched form of psychotherapy. CBT integrates two originally separate theoretical approaches, namely the cognitive approach and the behavioral approach, both of which are briefly outlined below. Indeed it is rather artificial to separate behavioral from cognitive procedures; most cognitive procedures contain behavioral techniques and most behavioral procedures also comprise cognitive elements (Emmelkamp, 2004).

According to cognitive theory, depressive people hold unrealistic negative views about themselves, their world, and their future (the negative cognitive triad). Characteristic of depression are the systematic distortions in information processing that leave sufferers unable to correct these maladaptive beliefs. In cognitive therapy, people are trained to systematically collect information to evaluate their maladaptive information-processing strategies and to conduct behavioral experiments to test the accuracy of their negative beliefs. Cognitive theory suggests that changing what people believe and the way they process information is the primary mechanism of change in cognitive therapy (Beck et al., 1979).

Behavioral approaches differ from cognitive approaches with respect to the role they ascribe to the various factors in the etiology and functioning of depression. Behavioral approaches attempt to change the maladaptive behavior by increasing positive reinforcement. This can be done through increasing activity level, enhancing social skills and problem solving training. Within behavioral models of depression, cognitions are seen as the result of depression. Accordingly, it is assumed that maladaptive cognitions will change as a result of the behavioral treatment (Emmelkamp, 2004). One important behavioral model is the operant model. This model is based on the assumption that depressive symptoms result from a low rate of response-contingent reinforcement and that depression will be improved when the rate of reinforcement for adaptive behavior is increased (Lewinsohn et al., 1976).

CBT, which incorporates both cognitive and behavioral models, has been proven effective in the treatment of depression and also in the prevention of relapse and recurrence (Hollon et al., 2006; Vittengl et al., 2007). It is not only CBT that is an effective treatment for depression, other psychotherapies are also effective, such as problem solving, behavioral activation, marital therapy and interpersonal psychotherapy (Barbato and D’Avanzo, 2006; Cuijpers et al., 2007c; Cuijpers et al., 2007d; Parker et al., 2006).

Despite the proven effectiveness of different psychotherapies, research shows that depression often remains untreated. In a large European survey of depression in the community it was found that a significant proportion of sufferers from depression (43%) failed to seek treatment for their depressive symptoms (Lepine et al., 1997). In a Dutch population study, more than half of the people with major depression (54.7%) did not receive professional help for their mental problems (Spijker et al., 2001). Most people with depression who do seek help for...
their symptoms, receive care in primary care settings (Bijl and Ravelli, 2000; Wang et al., 2007). Despite this, many depressed people remain unrecognised (Tiemens et al., 1996). Even when the depressive symptoms are identified, many primary care patients do not receive the care they need (Katon et al., 2004; Simon et al., 2004).

Important reasons for not receiving care is the absence of a perceived need for care and peoples’ own failure to recognize that their problems have a mental health origin (Verhaak et al., 2009). Other reasons are, for example, refusal of medication or poor compliance with pharmacotherapy (Simon et al., 1993) or the non-feasibility of effective psychotherapies in primary care. Undertreatment might also be a consequence of various barriers, like a shortage of skilled therapists, long waiting lists and high costs of psychotherapy. More personal barriers to consulting a therapist include the idea that “talking” does not help, lack of willingness to talk to a stranger about personal problems, and fear of stigma (Cuijpers, 1997; Prins et al., 2008). Therefore, we are challenged with developing (cost-) effective treatments for depression that can overcome these barriers and can reach people who are not being reached within the current healthcare system.

**Internet-based treatment**

With regard to the effects of psychotherapy there is a long history of investigating different methods of treatment delivery, including individual, group, telephone, book, DvD and computer-delivered CBT. The most recent development is to use computers and the Internet in the treatment of psychological disorders.

Internet usage is increasing rapidly: 26% of the world’s population has access to the Internet which represents a growth of 380% over the past nine years (Internet World Stats). There are large differences in internet penetration. For example, 52% of the European population has access to the Internet and 74% in North America. In the Netherlands the penetration rate is relative high at 86%. Searching for health information on the Internet is common (Baker et al., 2003). As a result, health care providers try to reach their target population by, for example, Internet-based treatments.

Defining Internet-based treatment can be problematic as the Internet can serve different functions in a treatment. Internet-based treatment may for instance include posting information available on websites. Information can also be given via video and audio files. Besides information exchange, interventions can make use of the interactive functions of the Internet, like structured self-assessments and communicating with a (virtual) therapist or with fellow sufferers. Different ways of communicating via the Internet are possible such as e-mail, chat, telephone or via discussion groups. Internet-based treatment can be a mix of all of this. Here, we use the following definition: “Internet interventions are treatments, typically behaviorally based, that are operationalized and transformed for delivery via the Internet. Usually, they are highly structured; self-guided or partly self-guided; based on effective face-to-face interventions; personalized to the user; interactive;
enhanced by graphics, animations, audio, and video; and tailored to provide follow-up and feedback” (Ritterband et al., 2006).

The potential of the Internet to deliver psychological treatments is considerable. The demand for traditional CBT for anxiety and depressive disorders exceeds the supply of suitably trained therapists. As a result, waiting lists are often long. Treatment via the Internet could be of value here. The Internet offers the opportunity for widely available, 24-hour access to treatment. It has the ability to reach people who cannot be reached within the traditional health care system. This is especially important for people with personal barriers to talking to a psychotherapist. People may prefer Internet-based treatment because of its anonymity. Furthermore, Internet-based interventions are likely to be cost-effective, although evidence on this is still scarce (Kaltenthaler et al., 2006; Titov, 2007).

Besides advantages, Internet-based treatment is accompanied by a number of limitations. First of all, not everyone has access to the Internet. In the Netherlands, Internet access is more common among higher educated people, higher-income families and families with children. People older than 65 years are less likely to have Internet access (Central Bureau of Statistics). Another limitation concerns websites with inaccurate or inappropriate health information which may result in harmful outcomes, such as inappropriate treatment or delays in seeking necessary medical care. Furthermore, privacy may be violated. Personal information that people enter into a web application could be misused for other purposes (Robinson et al., 1998).

A major issue is whether it is better to offer Internet-based treatment with the support of a coach or whether automated programs might work. Where support is given it is not clear which level of support is needed. The support can vary from automatically generated messages to personalized feedback. Support can be given by e-mail, telephone, chat or mobile phone (Titov, 2007).

There is growing evidence that Internet-delivered CBT can be an effective way of treating depression, although it’s not clear under which circumstances positive effects can be achieved. For example, in their first study, (Clarke et al., 2002) found that Internet-based CBT as pure self-help did no better than care as usual in reducing depressive symptoms. When telephone reminders were used to increase adherence to the treatment, CBT outperformed the control group in reducing depression (d = .28) in the second study (Clarke et al., 2005). In a trial with guided CBT and a waiting list control group, a high between-group effect size (d = 0.90) was found for depression (Andersson et al., 2005). Also, positive effects have been found for online CBT and psycho-education combined with weekly telephone contacts; both were more effective in reducing symptoms of depression than an attention placebo (Christensen et al., 2004). In another study the same authors found that brief CBT was not as effective as an extended version of CBT (Christensen et al., 2006). There are indications that online support is important for treatment adherence and outcome, as was shown in recent meta-analyses (Andersson, 2009; Spek et al., 2007a), although unguided Internet-based CBT did
produce better results than a waiting list control group (d = .55) in older adults (Spek et al., 2007c). In a primary care setting it was shown that Internet-based CBT with support was more effective than usual care by a general practitioner in mild to moderate depression and anxiety (Proudfoot et al., 2003). In the Netherlands, unguided Internet-based CBT did not outperform care as usual and the combination of unguided CBT and care as usual (de Graaf et al., 2009). Studies evaluating the long-term effects of Internet-based CBT are scarce but promising (Mackinnon et al., 2008; Spek et al., 2008a).

Most Internet-based treatments are based on CBT because of its effectiveness with depression (Hollon et al., 2006). Its structured format and clear conceptualization makes it very suitable for self-help purposes. It is unknown whether other formats than CBT are also effective. As has been shown in recent meta-analyses, traditional problem solving therapy (PST) is effective in treating people with various mental health problems and with depression (Cuijpers et al., 2007d; Malouff et al., 2007). It is not known, however, whether Internet-based PST also works with depression. Therefore it would be valuable to study Internet-based PST and compare it with Internet-based CBT.

Internet-based treatment in a broader perspective

Internet interventions are not only being used for the treatment of depression but for other (mental) health problems as well. Research shows that Internet-based self-help is effective for treating various anxiety disorders (Spek et al., 2007a; van't Hof et al., 2009) smoking (Myung et al., 2009) and other health problems like pain and headache (Cuijpers et al., 2008a). Other targets of Internet interventions include, for example, obesity (Krukowski et al., 2009), insomnia (Ritterband et al., 2009) and physical activity (van den Berg et al., 2007).

In this thesis, one of these target areas, namely Internet-based treatment for smoking cessation, is explored further. The effectiveness of treatment via the Internet for people who want to quit smoking was recently confirmed in a meta-analysis (Myung et al., 2009). A research area that needs attention is the question for whom Internet-based treatment for smoking cessation works best. Studying predictors of smoking cessation outcomes can help identify for whom current Internet interventions are most effective and for whom we need to further modify current interventions. This question is examined in a separate study.

Working mechanisms and predictors

A question that has fascinated researchers for a long time is whether all traditional psychotherapies are equally efficacious. Results are mixed. Earlier meta-analyses suggested that cognitive behavior therapy is more efficacious than other types of psychological treatment for depression (Dobson, 1989; Gloaguen et al., 1998), although this finding is not supported by other meta-analyses (Cuijpers et al., 2008b; Wampold et al., 2002). The latter study found no large differences between
the major types of psychotherapy. Although interpersonal psychotherapy was somewhat more efficacious than other psychological treatments and nondirective supportive therapy was somewhat less efficacious than the other treatments. In short, it’s not a foregone conclusion which treatment is most effective. The absence of significant differences between most of the major types of psychotherapy may be seen as support for the “Dodo Bird Verdict” that says that all psychotherapies are equally efficacious and “all should have prizes” (Luborsky et al., 1975). Although the efficacy is comparable, this does not imply that these were realized by the same mechanisms.

The issue of identifying the mechanisms of change in psychotherapy for depression has been a research area for many years, especially for CBT, given its established efficacy. Identifying the working mechanisms has important theoretical implications regarding answers to the questions of how, for whom, and under what set of circumstances psychotherapy produces positive outcome. Moreover, identifying the critical ingredients of change may have important clinical implications in regard to ways to maximize treatment efficacy. In the search for these active ingredients, investigators have tried to identify the mediators of change in CBT with depression. A mediator is the variable through which the independent variable influences the dependent variable of interest.

Yet, uncertainty remains as to the specific mechanisms by which CBT exerts its therapeutic effects (Garrett et al., 2007; Longmore and Worrell, 2007; Oei and Free, 1995; Whisman, 1993). Even reviews show mixed results. One review evaluating cognitive processes in cognitive therapy for depression indicates that most research generally supports cognitive mediation (Garrett et al., 2007) whereas another review concluded that there is little empirical support for the role of cognitive change as causal in the symptomatic improvements achieved in cognitive behavior therapy (Longmore and Worrell, 2007). Comparing the findings of the recent reviews with those of a similar, older, review (Whisman, 1993), it seems that progress in this area has been slow. Besides CBT, research directed at evaluating the working mechanisms of treatment for other forms of psychotherapy is almost absent.

In addition to identifying mechanisms of change during psychotherapy, investigators have examined the potentially predictive influence of client characteristics on the outcome. A variable that predicts outcome irrespective of the treatment is often referred to as a predictor. A variable that predicts a different pattern of outcome between two or more treatments is called a moderator (Kraemer et al., 2002). Most prior research has examined the relationship between outcome and predictors. A recent article provides an overview of findings on the association between sociodemographic factors and depression characteristics on the one hand and outcomes of pharmacotherapy, cognitive-behavioral therapy, and interpersonal/psychodynamic psychotherapy for major depression, on the other hand (Van et al., 2008). In this review, the impact of predictors for pharmacotherapy and psychotherapy respectively is assessed separately. For psychotherapy it was found that marital status may be related to better outcome in
the case of CBT, but not in interpersonal psychotherapy. Longer duration of depression was negatively related to outcome in psychotherapy in general. The relationship between severity of depression and outcome appeared to be complex, partly depending, on different outcome definitions across studies (Van et al., 2008). These results are partly in accordance with a review about cognitive therapy of depression (Hamilton and Dobson, 2002) in which poorer response was also associated with high chronicity and marital status. Alongside these predictors, they found that high pre-treatment severity scores, high pre-treatment levels of dysfunctional attitudes, younger age at onset, an increased number of previous episodes predicted poorer response.

For Internet-based treatment, research into working mechanisms is still a neglected issue. In addition, studies about possible predictors of outcome of Internet-based treatment for depression have just begun. For example, one study investigated predictors of outcome of group versus Internet-based CBT for depression (Spek et al., 2008b). They found that higher baseline depression scores, female gender, and low neuroticism predicted better outcome for both group and Internet-based CBT for depression. Altruism (as a personality factor) was related to outcome only in the group treatment. In another study in which Internet-based CBT for depression was assessed, the use of medication was highly predictive of a negative long-term outcome (Ruwaard et al., 2009). In sum, we have limited knowledge on predictors of outcome making it difficult to state for whom Internet-based treatment is suitable.

**Aims and research questions**

Several issues concerning Internet-based treatment for depression remain unsolved. One issue is whether other forms of Internet-based treatment than the ones based on CBT are also effective. And whether different forms of Internet-based treatment work equally well. Another issue that needs to be addressed is whether Internet-based treatment is a cost-effective intervention in relation to a comparison group. Other unsolved issues concern for whom Internet-based treatment works best and the underlying working mechanisms of these treatments. These questions gave us good reason to perform our research in a randomized controlled trial.

The main aim of this thesis is to study the effectiveness of Internet-based CBT and Internet-based PST compared with a waiting list control group. Both treatments are studied as Internet-based self-help interventions combined with support. Secondary aims of the study are the evaluation of the cost-effectiveness of both treatments, identifying potential mediating variables that could explain the outcome and establishing predictors of treatment success. The bulk of the current thesis relates to the main study, our randomized controlled trial. In addition, we performed a separate study: the evaluation of predictors of outcomes in Internet-based interventions for smoking cessation.
Outline

Chapters 2 to 6 contain results based on data from our randomized controlled trial. Chapter 2 describes the protocol of this study. The recruitment, the sample, the procedure, the outcome measures and the planned statistical analyses are described. Chapter 3 presents findings regarding the clinical effectiveness of both Internet-based treatments compared with the control group and the differences between the two treatments. This study focuses on short-term (clinically significant) effects. Chapter 4 contains an economic evaluation of both Internet-based treatments. The evaluation deals with cost-utility as well as cost-effectiveness. Differences between the two treatments in terms of cost-effectiveness are described. Chapter 5 addresses the working mechanisms of both treatments. Predictors of treatment success are discussed in Chapter 6. Chapter 7 is not related to our randomized controlled trial. Instead, in this section predictors of outcomes in Internet interventions for smoking cessation are examined. Finally, Chapter 8 presents a general discussion of the results related to the main study including a description of clinical implications and directions for future research.