Web-based cognitive behaviour therapy for depression in adults with Type 1 or Type 2 diabetes

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*World Diabetes Day (WDD) - each year on the 14th of November - is the primary global awareness campaign of the diabetes. It was introduced in 1991 by the International Diabetes Federation (IDF) and the World Health Organization (WHO) in response to the alarming rise in diabetes around the world. In the Netherlands WDD is organised by Platform Wereld Diabetes Dag. In 2010, the Dutch WDD was characterised by the photocontest Diabetes 24/7. All photographers in the Netherlands, both amateurs and professionals, were invited to portray diabetes in all its facets. This resulted in over 300 touching and striking images. More information: www.werelddiabetesdag.nl, www.diabetes24-7.nl and www.worlddiabetesday.org.
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Web-based cognitive behaviour therapy for depression in adults with Type 1 or Type 2 diabetes

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Voor mijn tante Mary
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CHAPTER 1

General Introduction
In this introductory chapter, light is shed on the main theme of this thesis: depression in diabetes patients. First, the global burden of both diabetes and depression are outlined, and a state of the art insight into evidence based treatment options for depression in diabetes patients is provided. Subsequently, the aim and outline of this thesis are described.

**Importance of this thesis**

This thesis focuses on depression, a common comorbid health problem in adult patients with type 1 or type 2 diabetes mellitus. Depression affects approximately 10-20% of the diabetes patients. Depression is known to have serious adverse effects, not only on the quality of life of diabetes patients, but also on their diabetes outcomes. To date, in longitudinal studies, depression in diabetes appeared to be associated with poor glycaemic control, more diabetes complications and higher mortality rates.\(^1\)\(^-\)\(^5\) For these reasons, it is of great importance that depression in diabetes is adequately treated.

**Background**

**Diabetes**

Diabetes mellitus, often simply referred to as diabetes, is a chronic metabolic disease, in which a person has diminished secretion or function of insulin, which results in high levels of blood glucose. Symptoms of poorly treated or untreated diabetes are, amongst others, polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger).\(^6\)

There are two main types of diabetes, type 1 and type 2 diabetes. Type 1 diabetes results from the body's failure to produce insulin due to autoimmune destruction of insulin producing beta-cells in the pancreas. Insulin is a hormone that is necessary for glucose uptake from the blood circulation into the cells of the body.\(^7\)

Type 2 diabetes results from insulin resistance and beta-cell dysfunction. In insulin resistance, cells become less sensitive to insulin. The pancreatic beta cells respond to this resistance by making extra insulin, which for a time keeps glucose in the normal range. Eventually this compensatory mechanism fails and blood glucose levels increase, leading to type 2 diabetes. Insulin resistance, however, can be reduced for example by weight lose and exercise and other life style changes.\(^7\)

Where type 1 diabetes usually has its onset at younger age (before the age of 25) type 2 diabetes is generally diagnosed after the age of 50. Another important difference between both types of diabetes, is that type 2 diabetes is strongly related to hereditary and life style factors.\(^8\) It often occurs in elderly, in people who have a relative with diabetes and in people suffering from overweight which is often related to an unhealthy lifestyle.\(^8\) Currently, type 2 diabetes accounts for 90% of all cases of diabetes.\(^8\)

**Global burden of diabetes**

Diabetes is a major health problem. Affecting about 286 million people worldwide, it is currently one of the most common non-communicable diseases globally.\(^9\)\(^-\)\(^11\) It is one of the leading causes of death in most high-income countries and there is substantial evidence that it is epidemic in many economically developing and newly industrialized nations.\(^9\)\(^-\)\(^12\) Therefore, the international initiative ‘Unite for Diabetes’ has been started by the World Health Organisation (WHO) and the International Diabetes Federation (IDF) aimed at raising awareness of diabetes, to engage the public and governments to tackle the disease and to help support a United Nations (UN) Resolution on diabetes. This UN resolution for diabetes was adopted on the 21st of December 2006.

In the Netherlands, currently over 800,000 people suffer from diabetes, with a major increase in incidence and prevalence between 1990 and 2007.\(^12\) Therefore, a
national initiative for prevention of the onset of (complications of) type 2 diabetes has been initiated by the Dutch government in 2009, the National Action programme Diabetes (Nationale Actieprogramma Diabetes, NAD). Aim of the 4-year NAD programme (2009-2013) is to create the conditions for achieving the government’s goals of reducing the incidence of diabetes and diabetes complications and to improve the care for diabetes patients.

**Treatment of diabetes**

The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), two landmark trials in large cohorts of type 1 and type 2 diabetes patients in the USA and Canada, and in the UK, have convincingly demonstrated that extreme high blood glucose levels are important risk factors for serious macro- and micro-vascular complications, such as coronary artery and peripheral vascular disease, stroke, diabetic neuropathy, and renal failure.\(^{14-17}\)

Diabetes complications can result in disabilities, such as fatigue, blindness and limb amputation, and in reduced life expectancy. On societal level, they result in reduced quality of life of the diabetes population, increased health care consumption and subsequent rises in health costs. Adequate treatment that results in optimal glycaemic control, has shown to significantly reduce the risk of complications and is therefore warranted.\(^{17}\)

Diabetes particularly designates itself from other chronic diseases, regarding its treatment, since diabetes treatment and care largely consist of self-care. Type 1 diabetes is treated with (self-injected) insulin or by insulin pump therapy. Patients have to measure their own blood glucose levels on average four times per day, after which they have to administer the appropriate amount of insulin themselves. Type 2 diabetes is often initially treated with diet and/or oral blood glucose lowering medication, but after several years this treatment is in the majority of the patients insufficient, due to natural progression of beta-cell failure. As a result, insulin injections are required to adequately control their blood glucose levels.

Diabetes is a largely self-managed disease, and poor glycaemic control is at least partly directly related to patients’ self-management behaviours.\(^{17}\) In order to achieve and maintain good glycaemic control, adherence to insulin or oral medication treatment is essential. Besides adequate glycaemic control via medication adherence, prevention of deteriorating factors and improvement in metabolism is important, via improvements in lifestyle habits, such as smoking cessation, physical exercise, healthy nutrition, and weight loss in patients with overweight.\(^{18-19}\)

In the Netherlands, the Dutch Diabetes Federation (Nederlandse Diabetes Federatie, NDF) published guidelines for diabetes treatment and care (health care providers and system) and self-care (patients), in the Diabetes Care Standard. Currently, the NDF studies the compliance with this Standard in patients and in health care providers.\(^{20-21}\)

**Psychosocial aspects in the treatment of diabetes**

Poor adherence to treatment and to healthy life style recommendations can seriously impair glycaemic control in diabetes patients and thus increase the risk of developing long-term diabetes complications. To understand patients’ self-care behaviour, we need to take into account various psychological and social factors. Adequate management of diabetes on a daily basis is not a simple task that can easily be achieved by education, i.e., knowing “what is right for you.” Clearly, knowledge is a prerequisite, but in no way a guarantee, of adhering to recommended treatment and lifestyle.\(^{22}\)

Behavioural research findings underscore the role of attitudes and illness beliefs as determinants of patients’ health behaviours. For example self-efficacy or
misperceptions regarding the seriousness and controllability of diabetes can inhibit active participation of the patient in the treatment. Also social support can influence patients’ self-care behaviours, e.g. a supportive partner or lack of understanding from children. In addition, contextual factors such as financial barriers to healthy lifestyle behaviours (e.g. healthy food, sports) and difficulty with access to health care (e.g. travelling distance and time, costs) or life style related programs (e.g. sports) influence peoples’ self-care behaviours. In diabetes care, a bio-psychosocial approach to the illness and coping problems, in which physical, psychological and social/contextual factors are being addressed, is warranted.21

Emotional distress of diabetes
Diabetes can have a major impact on the lives of patients and their families. As mentioned earlier, coping effectively with the stresses related to daily diabetes management, can improve quality of life.24 25

Besides diabetes treatment, fluctuating blood glucose levels themselves add to the stress of living with diabetes. Hyperglycaemia for instance is associated with reduced energy levels and poorer cognitive functioning, while hypoglycaemia is associated with difficulties in performing cognitive tasks, mood changes and loss of consciousness.26-28 Thus, hyper- and hypoglycaemia often contribute to emotional distress and can lead towards a lower emotional well-being. Also, diabetes-specific anxieties can occur, such as fear of hypoglycaemia, and fear of insulin injection.

An instrument has been developed to measure to what extent patients suffer emotionally from their diabetes, the Problem Areas in Diabetes Scale (PAID), a 20-item self-report questionnaire which has four subscales: negative emotions, treatment problems, food-related problems, and lack of social support.24 Currently, this instrument is used frequently in both research and clinical practice.

Studies have shown that patients who suffer from elevated diabetes-specific emotional distress, more frequently suffer from depressive symptoms or a depression.24

Depression
Depression is a mental disorder, characterized by two core symptoms: an all-encompassing low mood (depressed mood) and loss of interest or pleasure in normally enjoyable activities (anhedonia), persisting for at least two weeks.29 Additional symptoms are: lack of energy, sleep disturbance, lack of concentration, changes in appetite (often resulting in weight changes), apathetic or agitated behaviour, negative feeling about oneself, and recurrent thoughts about death and/or suicide. At least one core symptom and four additional symptoms must be present to meet the diagnosis major depressive disorder (MDD) of the Diagnostic and Statistic Manual of Mental Disorders (DSM-IV-TR).29 Depression is a disabling condition which adversely affects a person’s quality of life, their family, work or school life, sleeping and eating habits, and general health.30

People suffering from subclinical (subthreshold) depression experience almost the same degree of impairment of health status, functional status, and disability as those diagnosed with MDD.31-33 People with subclinical depression have elevated depressive symptoms, but do not meet the DSM-IV criteria for MDD.34 35
Global burden of depression
Depression has been acknowledged to be a major health problem. It is estimated that 5-10% of the population at any given time is suffering from identifiable depression needing psychiatric or psychosocial intervention. The life-time risk of developing depression is 10-20% in females and slightly lower in males.36

Depression often recurs. Patients who had had one episode of depression, show relapse in fifty percent of the cases and even a higher percentage relapses when having experienced more than one episode (two episodes, seventy percent; three or more episodes, ninety percent).37

The economic costs that are being caused by depression, both MDD and subclinical depression, are considerable, in terms of direct (e.g. medical care) and indirect costs (e.g. loss of work (productivity)).33,38

Treatment of depression
Psychotherapy and pharmacotherapy are both effective treatment options for major depressive disorder (MDD), each having its own merits, while in mild to moderate severe depressive symptoms there is little to no evidence for the effectiveness of pharmacotherapy.39-42 Anti-depressive medication (AD) is assumed to recover the natural balance between neurotransmitters often by increasing serotonin and noradrenaline levels, thus resulting in a new chemical balance, which often results in diminished depressive symptoms.43 In severe cases AD is often offered in combination with psychotherapy.39-42

Several forms of psychotherapy for treatment of depression have been developed, such as cognitive behavioural therapy (CBT), problem solving therapy, psychodynamic therapy, and interpersonal psychotherapy. CBT has been proven effective in numerous studies and is therefore evidence-based.44-45

CBT is based on the A-B-C-model which assumes that not merely an event or adversity (A) contributes to disturbed and dysfunctional emotional and behavioral consequences (C), but the dysfunctional beliefs (B) about the event (A) are the main cause of depressed feelings (C). For example it is not measuring a poor blood glucose that makes a patient distressed, but it’s the thought “It’s no use, I will never be able to manage my diabetes, I’d rather give up” that makes the patient feel distressed. These dysfunctional and irrational thoughts can lead towards dysfunctional behaviours, e.g. not measuring blood glucose anymore.46-47

By addressing and changing these dysfunctional thinking patterns and subsequent dysfunctional behaviour, which are characteristic of depressed patients, depression can be treated effectively. In the given example a patient learns to recognise his/her dysfunctional thoughts when measuring poor blood glucose. Consequently, he or she learns to come up with an alternative functional cognition, e.g. “Okay, I measured an elevated blood glucose level, but that can happen once in a while, it’s not a disaster, this means that there is room for improvement” and accordingly would proceed with his/her treatment effort.

The behavioural part of CBT relates to behavioural activation, social skills training and assertiveness training.

Lewinsohn (1995) developed the evidence based CBT course, the Coping with Depression Course (CWD), which includes cognitive restructuring, a social skills training, increasing pleasant activities, and relaxation.48 49

The CWD can be administered as a self-help book, a group intervention or in face-to-face therapy. Following the most recent societal development of the emerging Internet, the intervention has recently also been made available as a self-help intervention on the Internet.50-51
Diabetes and depression

Overall, studies have demonstrated that individuals with diabetes are more likely to have depression than those without diabetes or those with no chronic disease. The odds of having depression in diabetes are doubled, compared with the general population, both on diagnostic interviews as on self-reported scales. The exact worldwide depression prevalence among individuals with diabetes is complicated by variations by diabetes type and among nations. Estimations based on a meta-analysis indicate a prevalence of depression of 26.1% in diabetes patients compared with 14.4% in a non-diabetes study population based on self-report scales, and 9.0% compared with 5.0% based on diagnostic interviews.

The causal pathway linking diabetes and depression is still unclear. There are three main hypotheses explaining the causal pathway between diabetes and depression.

First, studies have shown that people with diabetes, both type 1 and type 2, are more likely to have incident depression than the general population (RR 1.15, 95% CI 1.02-1.30). This implies that having diabetes is a risk indicator for incident depression (see Figure 1, arrow 1). The emotional burden of living with diabetes may account for this.

More than 300 years ago, Thomas Willis, a British physician, observed that “diabetes frequently occurs in persons who experienced periods of sadness or long sorrow.” Thus, Willis was the first to formulate the second hypothesis, i.e., that depression causes or contributes to the development of diabetes (see Figure 1, arrow 2). This hypothesis has been confirmed in several studies, finding a 37% - 60% increase of incident type 2 diabetes in depressed patients.

The underlying mechanism explaining hypothesis 2 is not clearly understood, but is believed to result from increased counter regulatory hormone release and action, alterations in glucose transport function and increased immune inflammatory activation.

![Figure 1](image_url)

Figure 1. Hypotheses explaining the causal relation between diabetes and depression

The third hypothesis assumes that there are underlying common denominators causing or contributing to both conditions, for example a genetic factor, foetal nutrition or childhood adversity, which increases the risk for developing both depression and diabetes (see Figure 1, arrows 3).

Additional research is needed to further delineate the relationship between depression and diabetes. What is important to mention, is that the three hypothesis are not mutually exclusive.

In terms of treatment it might be of importance how depression is related to the diabetes. When depression is caused by the emotional burden of diabetes (hypothesis 1), coping with diabetes-related issues seems of importance in depression treatment, while not necessary when the two illnesses are causally unrelated.
Consequences of depression in diabetes outcomes
Depression is known to be associated with suboptimal diabetes outcomes. Studies have shown a significant relationship between depression and poor adherence to diabetes treatment regimens, such as healthy life style behaviour, diabetes self-management and medication taking. Diabetes patients who suffer from a co-morbid depression are more often in poor glycaemic control, and show higher complication rates, are at greater risk of disability, show reduced work productivity, lower quality of life and die younger. As would be expected use and therefore costs of healthcare are higher for people with diabetes and coexisting depression.

Recognition and referral of depression in diabetes patients
The fact that in the Netherlands the majority of diabetes patients periodically visit their treating physician, either in primary, secondary or tertiary care, provides the unique opportunity to screen these patients for depression and to adequately refer them for depression treatment. However, studies have indicated that recognition of depression is far from optimal in both primary and secondary care settings.

There are several barriers that impede on early recognition, adequate referral and thus adequate treatment of depression. These barriers are related to the health care system (accessibility to mental health care, travelling time, distance, costs, the division of mental and somatic health care), physicians (e.g. insufficient recognition of symptoms of depression or inadequate referral), and by patients (underrepresentation of depressive symptoms, negative stigma of psychological treatment, feeling of shame for needing psychological help, idea that treatment would not help). There is a need for effective strategies to increase early recognition of depression, the availability of evidence-based interventions, and adequate referral to such interventions.

Treatment of depression in diabetes
Evidence suggests that treatment of depression in people with diabetes is both efficacious and cost effective and may result in improved overall diabetes outcomes. A recent meta-analysis showed that depression in people with diabetes can be treated effectively with anti-depressant medication, psychotherapy or combined therapy, with possible benefits on diabetes outcomes such as glycaemic control. Psychotherapy shows highest effect sizes \( (d = -0.58; 95\% \text{ CI } -0.77 \sim -0.39 \text{ compared with } d = -0.47; 95\% \text{ CI } -0.67 \sim -0.27 \text{ for anti-depressant medication and } d = -0.29; 95\% \text{ CI } -0.43 \sim -0.16 \text{ for collaborative care}) \) in this meta-analysis.

The majority (56.7\%) of depressed patients with diabetes experience high levels of emotional distress directly related to diabetes. It therefore seems advisable to address disease-specific emotional distress in depression treatment. This could improve effect sizes and increase the beneficial impact on diabetes outcomes. In contrast with pharmacotherapy, psychotherapy lends itself for addressing diabetes-specific issues in treatment.

On these grounds, we have adapted an existing online depression intervention to the specific needs of diabetes patients, which resulted in a diabetes-specific depression treatment. We were the first to develop a diabetes-specific depression treatment. The intervention is primarily based on a cognitive behavioural therapeutic intervention. Examples of diabetes-specific topics that were incorporated in the intervention are: coping with fluctuations in blood glucose levels, coping with (worries about) complications, and communicating with health care professionals. The inserted topics were based on patient advice, professional advice, an existing CBT group program for diabetes-specific distress, and on literature.
Web-based therapy

In The Netherlands, we have seen an increase of internet use in the past years, with about 83% of the households currently being "online". In accordance with these developments in society, (mental) health interventions are increasingly offered through or supported by the Internet, varying from patient health information, electronic patient records, through education and psychological interventions, often referred to as eHealth.

Using the Internet to deliver psychological treatment can overcome barriers related to time restrictions, immobility, and geographical distance and thus increase reach and facilitate access to effective depression treatment, against relatively low costs.99-101

A meta-analysis showed that web-based CBT is an effective treatment for depressive symptoms.101 A Dutch, web-based version of Lewinsohn’s CBT self-help program, has shown to be effective in reducing depressive symptoms.97 103-104

eHealth in Diabetes

Depression affects at least 20,000,000 diabetes patients worldwide.8 There are simply not enough therapists to treat this number of patients, and in case enough therapists were available, this would be far too expensive for societies. Delivering anti-depressant therapy via internet is therefore a very attractive, relatively cheap alternative. Furthermore, specifically in diabetes patients, delivery of interventions via the Internet can be feasible since it can be done by patients in their own time and place. Impaired mobility due to chronic diabetes complications and already spending much time in health care can be diabetes-specific reasons for preferring therapy via the Internet instead of classical “face-to-face” therapy.

This, together with the high reach of Internet and the scope of the problem of diabetes might account for wide variety of eHealth that has been developed for diabetes patients. E-Health varies from information on diabetes through diabetes education programmes,105-106 diabetes self-management programmes,107-112 internet support groups,113 blood glucose monitoring programmes,119 114 and coping skills programmes.115-116

Aim and outline of this thesis

Considering the prevalence of diabetes and the high occurrence of co-morbid depression and a low availability of diabetes-specific depression treatment, we developed a web-based diabetes-specific depression intervention. This intervention is based upon the Dutch web-based version of Lewinsohn’s CBT self-help program.26 51

The main aim of this thesis is to study the effectiveness of this web-based Cognitive Behavioural Therapeutic (CBT) depression intervention in adults with type 1 or type 2 diabetes. Besides the effect of the intervention on depressive symptoms (primary outcome), the additional effects on diabetes-specific emotional distress and glycaemic control (secondary outcomes) are being examined.

Furthermore, since depression treatment has not indisputably shown to lead to improvements in glycaemic control, and since a substantial part of diabetes patients suffer from diabetes-specific emotional distress, it might be that depressive symptoms are not directly related with glycaemic control, but this relation is mediated by diabetes-specific emotional distress. This issue is studied in this thesis.

Before the effectiveness of the web-based intervention are reported, the study design will be described. Subsequently, the development and reach of the intervention is described. After having described the effectiveness of the intervention, the next step was to examine whether the intervention was more or less effective in patients
suffering more severe psychological problems (i.e. effect-modification by diagnosed MDD, diagnosed anxiety disorder and diabetes-specific emotional distress).

Thus, the research questions addressed in this thesis are the following:

1. How are depressive symptoms and diabetes-specific emotional distress related to glycaemic control?
2. How to develop a web-based diabetes-specific depression intervention?
3. Which patients do we reach with a study on a web-based diabetes-specific depression intervention?
4. Is a web-based diabetes-specific depression intervention effective in adult type 1 and type 2 diabetes patients in reducing depressive symptoms (primary outcome), diabetes-specific emotional distress and improving glycaemic control (secondary outcomes)?
5. Is a web-based diabetes-specific depression intervention more or less effective in certain subgroups of patients?

The general outline of the thesis is as follows: Chapter 2 presents the study protocol, which explains how the effectiveness of a web-based depression intervention in adults with type 1 and type 2 diabetes will be tested in a randomised controlled trial. In Chapter 3, the difference between diabetes-specific emotional distress and depressive symptoms, in relation to glycaemic control is explored in data collected within the framework of a depression in diabetes screening study (answers question 1). In Chapter 4, the development of the intervention is described as well as the inclusion of our study participants (question 2 and question 3). In Chapter 5, the results of the randomised controlled trial testing the effectiveness of the web-based intervention is presented (question 4). In Chapter 6, we closely examine effect modification of severe mental health problems in the effect of the web-based intervention: patients are compared with or without diagnosed major depressive disorder (MDD), diagnosed anxiety disorder, or elevated diabetes-specific emotional distress (DM-distress) (question 5). Finally, Chapter 7 provides the conclusion of this thesis, a general discussion on the results found in this thesis, implications for clinical practice and recommendations for future research.
CHAPTER 2

Web-based cognitive behavioural therapy (W-CBT) for diabetes patients with co-morbid depression:

Design of a randomised controlled trial

Abstract

Background Depression is common among people with diabetes, negatively affecting quality of life, treatment adherence and diabetes outcomes. In routine clinical care, diabetes patients have limited access to mental health services and depression therefore often remains untreated. Web-based therapy could potentially be an effective way to improve the reach of psychological care for diabetes patients, at relatively low costs. This study seeks to test the effectiveness of a web-based self-help depression programme for people with diabetes and co-morbid depression.

Research design and methods The effectiveness of a web-based self-help course for adults with diabetes with co-morbid depression will be tested in a randomised trial, using a wait-list controlled design. The intervention consists of an 8-week, moderated self-help course that is tailored to the needs of persons living with diabetes and is offered on an individual basis. Participants receive feedback on their homework assignments by e-mail from their coach. We aim to include 286 patients (143/143), as power analyses showed that this number is needed to detect an effect size of 0.35, with measurements at baseline, directly after completing the web-based intervention and at 1, 3, 4 and 6 months follow-up. Patients in the control condition are placed on a waiting list, and follow the course 12 weeks after randomisation.

Primary outcomes are depressive symptoms and diabetes-specific emotional distress. Secondary outcomes are satisfaction with the course, perceived health status, self-care behaviours, glycaemic control, and days in bed/absence from work. Questionnaires are administered via the Internet.

Discussion The intervention being trialled is expected to help improve mood and reduce diabetes-specific emotional distress in diabetes patients with depression, with subsequent beneficial effects on diabetes self-care and glycaemic outcomes. When proven efficacious, the intervention could be disseminated to reach large groups of patients with diabetes and concurrent depressive symptoms.
Background
Depression has been shown two times more prevalent among persons with type 1 or type 2 diabetes, compared to the general population.\textsuperscript{52} Approximately 10% of the adult diabetes patient population suffers from major depressive disorder and another 10% from minor depression.\textsuperscript{52} Data also suggest depression to be more persistent and recurrent in people with diabetes.\textsuperscript{117} The costs of depression in diabetes are known to be high, not only in terms of suffering and reduced quality of life, but also in view of adverse medical outcomes (e.g. hyperglycaemia, diabetes complications), and societal and economic costs.\textsuperscript{81-92}

Based on evidence to date, psychological therapy (particularly cognitive behaviour therapy, CBT) is the treatment of choice for depression.\textsuperscript{118} Only a few randomised controlled studies have been conducted to test the efficacy of antidepressant therapies in persons with diabetes and co-morbid depression.\textsuperscript{119-121}

Not surprisingly, depressive symptoms are likely to co-occur with high levels of diabetes-related emotional distress, as was confirmed in a recent international study.\textsuperscript{90} While the optimal treatment for depression in diabetes is still being sought,\textsuperscript{90} there is good reason to assume that the efficacy of anti-depressant psychotherapy in diabetes can be enhanced when specific issues associated with the burden of living with this chronic disease are adequately addressed.\textsuperscript{94}

We recently conducted a study to test the effectiveness of a group Cognitive Behaviour Therapy (CBT) developed for patients in prolonged poor glycaemic control in a RCT, and found CBT to be most effective in patients who entered the study with elevated depression scores.\textsuperscript{95-122}

Offering diabetes-specific CBT to diabetes patients with depression should thus be able to improve psychological health, self-management behaviours and subsequent medical outcomes. However, access to psychological services is limited, both in primary and secondary routine diabetes care.\textsuperscript{93} As pointed out by Glasgow et al.,\textsuperscript{123} we need to consider ways to enhance dissemination of effective psychological interventions to persons with diabetes. In this context, we believe use of modern interactive technology, such as internet-based therapy should be considered. More so, since web-based psychological interventions have shown their utility across a range of problem areas and are likely to be cost-effective.\textsuperscript{124-125}

Web-based cognitive behaviour therapy (W-CBT) is recognized as an effective treatment option for depression and appeared to be well appreciated by patients.\textsuperscript{101-125,128} In The Netherlands, we have seen an increase of internet-use in the past years, with about 83% of the households currently being "online".\textsuperscript{98} Internet-based therapy therefore has great potential to reach large groups of diabetes patients with co-morbid depression. To our knowledge, we would be the first to test the effectiveness of diabetes-specific on-line CBT for depression in persons with diabetes.

Aims of the Trial
This study aims to test the effectiveness and appreciation of web-based cognitive behavioural therapy (W-CBT) for adult diabetes patients with depression in a randomized controlled trial. The experimental condition will be compared with a waiting-list control group. It is hypothesized, that W-CBT will be well-received by the participants and will appear to be significantly more effective than the control condition in reducing levels of depressed mood and diabetes-specific emotional distress, with subsequent positive effects on self-management behaviours and glycaemic control on the longer term.
Research design and methods

Study Design
We chose a two-arm randomised controlled trial (RCT) design; including 286 patients (143/143) [see power calculation]. Measurements are scheduled at six points in time in the intervention group: at baseline, directly after completing the web-based intervention, and at 1, 3, 4 and 6 months follow-up. In the control group the same six measurements are scheduled with two additional measurements at 8 and 12 weeks after randomization (see flow chart, Figure 1).

Study procedures
The recruitment and screening procedure has been developed, so that patients interested in joining the study can visit the research website. There, the patient will be invited to read the study information and provide written informed consent. After receipt of the consent form, the patient will receive a password per e-mail allowing him/her to log in and complete the online screening questions. For the baseline measurement, patients are invited to fill out a booklet of questionnaires on the Internet, -which will take approximately 30 minutes-containing demographic data, in - and exclusion criteria, and depressive symptoms (Center for Epidemiological Studies Depression scale (CES-D) >16). If a patient does not qualify, this is explained and the patient is advised to contact his/her GP for further advice. If eligible, the patient will be interviewed by telephone using the Composite International Diagnostic Interview (CIDI). Data from this CIDI interview will be used to specify type of mood disorder (DSM-IV). Those with bipolar disorder, depression with psychotic features and patients who suffer from current suicidal ideation will be excluded. After eligibility is confirmed the patient is enrolled in the study.

Treatment allocation
Randomisation by computer will assign individual patients to either the experimental or control condition.

Recruitment
The on-line depression course will be delivered through a website. The study will be advertised in the Netherlands and Flanders (Dutch speaking part of Belgium) in clinics (e.g. hospitals, GP’s, pharmacy’s, rehabilitation centres) and through various media (e.g. patient journals, specialist journals, websites, e-mails, flyers, newspapers etc.). It will be advertised as a web-based course for persons with diabetes (type 1 or type 2) to help improve a depressed mood. Patient information on the study will be available on the research website. Inclusion and exclusion criteria will be stated clearly on this website.

Study population
The source population consists of adult diabetes patients with co-morbid depression. Blinding of subjects will - due to ethical reasons - not be carried out.

Inclusion criteria are: ≥18 years of age; having type 1 or type 2 diabetes (diagnosed > 3 months prior to study by a physician); having a depressed mood, as indicated by a score of 16 or higher on the Center for Epidemiological Studies Depression scale (CES-D); depression diagnosed by the CIDI-interview; having access to the Internet at home and having an e-mail address.

Exclusion criteria are: not having easy access to the Internet, reading problems (e.g. due to insufficient Dutch language skills, visual impairments or illiteracy); currently taking anti-depressant medication; a history of suicide attempt(s); current suicidal ideation (measured with the CIDI); bipolar disorder (CIDI); co-morbid organic psychiatric disorder (CIDI); loss of significant other < previous 6 months; or pregnancy.
Study design

CHAPTER 2

Figure 1. Flow chart of participants. AD: anti-depressives; CES-D: Center for Epidemiologic Studies Depression scale; PAID: Problem Areas In Diabetes scale; ADSCI: Diabetes Self-care Inventory; SF-12: Short-Form-12; EQ-5D: Euroqol 5D; CBT: Cognitive behavioural therapy
Description of interventions

**Intervention group**

Patient enrolment will occur individually on a continuous basis, i.e. at any point in time during the study period. The number of included participants is not limited by physical capacity other than the number of coaches available. After inclusion criteria are met and the patient has returned the informed consent s/he will be randomly assigned to the intervention or the control group.

Patients assigned to the intervention group will receive a password per e-mail with which they can log in to the course. They will be instructed (and reminded per e-mail) to complete one session per week, during 8 consecutive weeks.

Coaches will send e-mails to participants as a way to encourage them to continue their efforts. Such reinforcement should help to keep patients on track with the course and lower the risk of drop-out. They also provide the participants with feedback on their homework assignments. It is clearly stated that coaches will not give advice on personal issues.

**Control group**

Control group patients will receive an e-mail in which they are informed of the randomisation result, which means they will start the course after 12 weeks. To reduce the risk of loss of interest; participants placed on the waiting-list will automatically receive weekly protocollised e-mails with motivating, positive feedback to enforce them to remain involved in the study.

After eight weeks they are invited per e-mail to fill in the questionnaires again. Twelve weeks after randomization patients will undergo a second screening (using the CES-D-score ≥ 16 as a first screener for depression and additionally the CIDI interview) to confirm depression. If still eligible, the patient is invited to follow the course. Patients, who do not qualify, i.e. show (spontaneous) remission, are excluded at this point. Patients who developed suicidal ideation during the 12 weeks waiting period, are offered the opportunity to have an appointment with a diabetes psychologist of the VU University Medical Centre or a colleague nearby in case the distance from the participant’s home to the VUMC should be problematic.

The effectiveness of the intervention is determined directly after completing the web-based intervention up till 6 months follow-up (see Consort flow chart in Figure 1).

If the depression has deteriorated at the end of the course, as indicated by the scores of the CES-D, a consultation with a diabetes psychologist at the VU Medical Centre is offered to the patient. In agreement with their General Practitioner a decision will be made about further treatment or hospitalization.

**Intervention development and trial design**

The Dutch version of the manual-based self-help course named ‘Coping with Depression’ (‘In de put, uit de put’) has been adapted as web-based intervention (‘Kleur je Leven’).\(^{49}\)\(^{130}\) This intervention has been adjusted further by our team to fit the needs of patients with diabetes (‘Diabetergestemd’). Based on our research, clinical experience and input from an expert panel of diabetes patients, the following topics were incorporated: managing ‘poor’ test results, uncertainty about blood glucose fluctuations and negative emotions, communication with health care professionals, talking about diabetes with others, the burden of daily self-management, and coping with diabetes-related worries (e.g. about hypoglycaemia and late complications). The course consists of 8 consecutive weekly lessons. The course will provide information, practice examples, exercises/self-tests and homework assignments. The web-based course is delivered on an individual basis. Patients weekly receive (protocollized)
feedback on their homework assignments from their coaches by e-mail. The coaches are psychologists and residents in clinical psychology from the department of Medical Psychology of the VU medical centre, supervised by the research team. An internet-based group forum, which will be moderated by our team, is offered to participants to give them the opportunity to share experiences, provide support and discuss issues related to depression and diabetes. In the forum, specific treatment issues (e.g. related to oral medication or insulin) may not apply to all participants, but this should not be problematic. Rather, the mix of disease types and experiences can serve to illustrate the common features of diabetes and depression (thoughts, emotions and behaviors), while respecting individual differences.

It will be clearly stated that during the course of the study, all participants are allowed to make use of additional mental health care services if they feel a need to do so.

**Outcome Assessment**

**Primary outcome measures**

Primary outcome measure is the level of depression, measured by the online administered self-reported depression questionnaire Center for Epidemiological Studies Depression scale (CES-D) at baseline, directly after completion of the course and at one and six months follow-up.

**Secondary outcome measures**

Secondary outcome measures are: diabetes-specific emotional distress (PAID), satisfaction with the course (self-developed questions), perceived health status (EQ5D and SF-12), diabetes self-care behaviours (Amsterdam Diabetes Self Care Inventory), self-reported episodes of hypoglycaemia and glycaemic control (HbA1c) retrieved from the patients’ medical charts via their physician.

**Covariates**

Additionally, information on potentially confounding factors and effect modifiers will be collected by means of self-report: socio-demographic data (age, gender, marital status, highest level of completed education, and current occupation), lifestyle issues (smoking, body mass index (BMI), substance/alcohol abuse), data on diabetes (type of diabetes, duration, treatment regimen, co-morbidity) and additional mental health care consumption.

**Statistical Analyses**

Analyses will be conducted according to the intention to treat principle. The data will be presented as categorical and continuous variables. Baseline characteristics will be compared for the intervention and waiting-list group using Student t-tests and χ²-tests. Analysis of variance (ANOVA) will be conducted with the CES-D (depression) as dependent variable, with two independent variables: time (within-subject) and group (between-subject). The same analysis will be performed with the PAID score (diabetes-related emotional distress) as dependent variable. Two analyses will be conducted. Firstly, the direct effect of the intervention will be determined. ANCOVA’s will be performed in order to test whether both groups have different scores on the CES-D, at different points in time, with correction for potential confounders at baseline. Secondly, pre-post measurements will be conducted of all participants who have received the intervention. This will be analysed by means of a longitudinal regression analysis, which will be performed using Generalized Estimating Equations (GEE), taking into account the correlational nature of repeated measures data within subjects, and securing minimal loss of patients due to incomplete data. Clinical effectiveness will be
calculated by the amount of people who after completion of the course have a score on the CES-D of ≤16. The effect size will be calculated using Cohen’s d.\(^{134}\)

**Power calculation**

The sample size was calculated using STATA, based on clinically relevant differences. Effect Sizes (ES) are calculated as the difference between the control group and the intervention group after the intervention, divided by the pooled standard deviation.\(^ {135}\)

With 100/100 patients the study is powered to detect an ES of 0.35 (one-sided), with a power of 80% (α = 0.05). Based on a meta-analysis, we may expect an ES of 0.5 to 0.6.\(^ {126}\) We anticipate 30% non-completion/exclusion, which will be compensated by over sampling (n = 268; 143 in each group).

**Discussion**

**Strengths and limitations**

To the best of our knowledge, this randomised controlled trial will be the first to test the effects of a web-based CBT self-help course for people with diabetes and co-morbid depression. The intervention builds on an existing course that has shown to be feasible and effective to help improve mood in the general population.\(^ {50}\) Our trial is sufficiently powered to allow for conclusions as to its short-term effectiveness (6 months). In view of the "lenient" inclusion and exclusion criteria we will apply, the study is expected to have high external validity.

An obvious limitation of this trial is the fact that only people with access to the Internet and sufficient computer skills can be included. Overall, an estimated 82% of the Dutch households are online in 2007, but access to Internet among the elderly is much lower\(^ {46}\) and as a consequence this group may therefore be under represented in our study.

Inclusion and exclusion criteria are clearly stated on the website. This has the potential disadvantage that people can pretend to have certain characteristics in order to qualify or they can deny having "exclusion criteria". However, this response tendency may be diminished by the fact that patients are being made aware that we inform their GP’s of their participation in the study and that we will be in contact with their treating physician concerning their HbA1c results.

As the post-treatment assessment will be done directly after treatment and up till 6 months follow-up, no conclusions can be drawn about the long-term effects of the intervention. Therefore, after 6 months, patients will be asked to give permission for supplemental follow-up measurements at one and two years after completion of the course. These results will be analysed at a later stage and are not part of this project.

Although web-based administration of questionnaires is widely used, we should remind ourselves that the psychometric properties of internet-administered questionnaires may not be equal to those of paper-and-pencil versions.\(^ {135}\) On the other hand, in an earlier study we have found that the paper-and-pencil and the computerised versions of a short psychological well-being questionnaire appeared to be equivalent.\(^ {136}\) The major difference appears to be that respondents are more honest and revealing when filling out via the Internet, resulting in a relatively higher reported level of symptomatology. We have therefore chosen to confirm or decline the diagnosis of depression by a telephone administered diagnostic interview (CIDI). Our study will show if such diagnostic procedure is required in future projects applying W-CBT in order to reduce the risk of 'false positives'.

Also the psychometric properties of the following on-line questionnaires will be examined and compared to the paper-and-pencil versions: the PAID, SF-12 and the ADSCL.
Study design

We hypothesise that improved mood will be associated with improved diabetes self-management and we will test whether W-CBT has favourable effects on self-reported diabetes self-care behaviours, using the Amsterdam Diabetes Self-care Inventory (ADSCI) that was developed by our team and used in previous trials. The psychometric properties of the Amsterdam Diabetes Self Care Inventory (ADSCI) have not yet been published, but a report on the validity and reliability of the scale is planned based on data file.

Ethical and practical considerations have led us to decide that all participants are allowed to use additional mental health care (MHC) services during the trial. Usage of additional services therefore is a potential confounder that will be measured and taken into account in the statistical analyses.

Drop-out is often a problem in web-based therapy trials. In adapting the generic coping with depression course to the needs of people with diabetes, we expect to reduce drop-out. In an attempt to further reduce the attrition rate, support e-mails will be sent out to participants by their coach, to encourage them to stay involved in the course. Likewise, those in the waiting list condition will receive e-mails aimed to maintain contact and encourage them to participate.

The study protocol was approved by the VU University Medical Centre ethics committee, which is certified by the Central Committee on Research involving Human Subjects in the Netherlands.

Future implementation

If this intervention proves to be effective in reducing depression and shows to be well appreciated by diabetes patients, further dissemination of the intervention is anticipated. An implementation and dissemination plan is under development.

This intervention could also be adapted to suit the needs of people who suffer from chronic diseases other than diabetes.
CHAPTER 3

Diabetes-specific emotional distress mediates the association between depressive symptoms and glycaemic control in Type 1 and Type 2 diabetes

Abstract

Objectives To investigate whether diabetes-specific emotional distress mediates the relationship between depression and glycaemic control in patients with Type 1 and Type 2 diabetes.

Research design and methods Data were derived from the baseline assessment of a depression in diabetes screening study carried out in three tertiary diabetes clinics in the Netherlands. Most recent glycated haemoglobin (HbA1c) measurement was obtained from medical records. The Centre for Epidemiologic Studies Depression Scale (CES-D) and Problem Areas in Diabetes scale (PAID) were used to measure depression and diabetes-specific emotional distress respectively. Linear regression was performed to examine the mediating effect of diabetes-distress.

Results Complete data were available for 627 outpatients with Type 1 (n = 280) and Type 2 (n = 347) diabetes. Analyses showed that diabetes-distress mediated the relation between depression and glycaemic control and not differently for both disease types. Post-hoc analyses revealed that patients depressed and distressed by their diabetes were in significantly poorer glycaemic control relative to those not depressed nor distressed [HbA1c 8.7 ± 1.7 vs. 7.6 ± 1.2% in those without depressive symptoms, 7.6 ± 1.1% in depressed only and 7.7 ± 1.1% in the distressed only, \( P < 0.001 \)]. Depressed patients without elevated diabetes-distress did not show a significantly increased risk of elevated HbA1c.

Conclusions In explaining the association between depression and glycaemic control, diabetes-specific emotional distress appears to be an important mediator. Addressing diabetes-specific emotional problems as part of depression treatment in diabetes patients may help improve glycaemic outcomes.
Introduction

It is now well established that people with Type 1 and Type 2 diabetes have a doubled risk for co-morbid depression, compared with healthy controls.\textsuperscript{52} The clinical relevance of this finding is underscored by the fact that depression in people with diabetes is associated with impaired quality of life,\textsuperscript{77} microvascular complications, cardiovascular disease and mortality.\textsuperscript{2, 130} Early recognition and treatment of depression in diabetes is therefore advocated.\textsuperscript{17, 139}

One of the mechanisms that may link depression to adverse health outcomes is poor glycaemic control. Effective depression treatment could thus impact positively not only on mood but also on physical health. However, studies which have examined the association between depression and glycaemic control have yielded contradictory results.\textsuperscript{1}

Interestingly, both depression and poor glycaemic control have been found to be significantly correlated with diabetes-specific emotional distress\textsuperscript{140} and diabetes-distress has been suggested to mediate the relationship between depression and glycaemic control.\textsuperscript{141, 142} Moreover, to date, psychological depression treatment has shown small but significant positive effects on glycaemic outcomes.\textsuperscript{141} We can speculate that the efficacy of psychotherapy for depression could be further improved by addressing emotional issues specifically related to the burden of diabetes. Lowering of diabetes-related distress might help to enhance diabetes self-management, thereby attaining better glycaemic control.

In this study, we tested the hypothesis that the association between depression and glycaemic control is mediated by diabetes-specific emotional distress, following Baron and Kenny’s mediator model.\textsuperscript{144} If our hypothesis holds to be true, this would have implications for understanding how depression impacts on glycaemic control in diabetes patients and its clinical management.

Research design and methods

Cross-sectional data were derived from the baseline assessment of a Dutch multi-centre randomized controlled trial, which was aimed at testing the effects of screening for depression, with subsequent written feedback to patient and physician. Details of this study are reported elsewhere.\textsuperscript{145} In this study, a random sample of 2055 Type 1 and Type 2 diabetes outpatients was drawn from patient registers of three tertiary diabetes clinics in the Netherlands: (i) 1000 outpatients of the VU University Medical Centre (Amsterdam), (ii) 555 of the Haaglanden Medical Centre (The Hague) and (iii) 500 of the Radboud University Medical Centre (Nijmegen).

Patients were excluded if they reported: (i) a history of suicide attempts, (ii) admission for inpatient treatment of depression more than once or (iii) to have been diagnosed with schizophrenia. This was carried out on the advice of the Medical Ethics Committee, in order to prevent these specifically vulnerable subgroups from being emotionally burdened. Written informed consent was obtained from all participants. Once written informed consent was received, questionnaire booklets were sent to be filled out at home and returned in pre-stamped envelopes. The study was approved by the medical ethics advisory committees of all centres.

Assessment of depression symptoms with the CES-D

Depression symptoms were assessed using the Centre for Epidemiologic Studies Depression Scale (CES-D), a well-validated self-report scale that asks respondents to indicate the frequency of occurrence of 20 symptoms of depression during the past week. The instrument uses a four-point Likert scale, ranging from ‘rarely or none of the time’ to ‘most or all of the time’. In our study, we used a cut-off score of 16 and higher. This cut-off score of 16 and higher is commonly used to indicate clinically significant
Assessment of diabetes-specific emotional distress with the PAID
Diabetes-specific emotional distress was assessed using the Dutch validated version of the Problem Areas in Diabetes scale (PAID).24 The PAID is a widely used 20-item self-report scale which measures negative emotions towards diabetes and its treatment (e.g. feelings of guilt, anger, frustration, worries and fear). Items are rated on a five-point Likert scale (0–4), ranging from ‘no problem at all’ to ‘a very serious problem’. Scores were transformed to a 0–100 scale, with a cut-off score of 40 used as indicating seriously elevated emotional distress. This cut-off score is commonly found to represent 1 standard deviation above the mean for both Type 1 and Type 2 diabetes patients.20

Glycaemic control
Glycated haemoglobin (HbA1c) values were derived from patients’ medical records, all assessed within 3 months prior to the study. HbA1c samples were analysed in the three centres using HPLC techniques [Tinaquant or Bio-Rad (Bio-Rad Laboratories, Hercules, CA, USA) in the Haaglanden Medical Centre; Menarini (Florence, Italy) in the VU University Medical Centre and the Radboud University Medical Centre]. All reported values are Diabetes Control and Complications Trial (DCCT)-aligned.

Statistical analysis
Statistical analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Group comparisons were analysed using Student’s t-test, analysis of variance (ANOVA) and χ²-test. A P-value of < 0.05 was considered to be statistically significant in all analyses. Using Baron and Kenny’s mediator model,144 the following sub-hypotheses were tested: (i) depression (CES-D) is significantly related to glycaemic control (HbA1c); (ii) CES-D is significantly related to diabetes-specific emotional distress (PAID); (iii) PAID is significantly related to HbA1c before testing our main hypothesis, as follows: (iv) the relationship between CES-D and HbA1c is significantly reduced when controlling for PAID. These hypotheses were all tested using linear regression analyses, the Sobel test was used to determine whether the mediating effect of diabetes distress was statistically significant.144 Sex, age, type of diabetes and body mass index were added to the model, to examine their confounding and/or mediating effects.

Results
Baseline characteristics
Out of 2055 patients invited to participate in the study, a total of 1803 (88%) patients responded to the invitation, of whom 1012 (56%) returned their baseline questionnaires. Analyses were performed using data of 627 patients (31% of those invited), who provided us with complete data on the depression and diabetes distress questionnaires and HbA1c. Non-completers had significantly lower level of education compared with completers and more often reported a non-Dutch background (P < 0.001). Baseline characteristics of n = 627 are presented in Table 1. Patients were mainly Caucasians, with 10% having a non-Dutch background (4% Surinamese, 2% Indonesian, 1% Turkish and 3% other). Mean age of patients with Type 1 diabetes (n = 280) was 44 ± 14 years, mean diabetes duration 22 ± 13 years and the most frequent diabetes complication was retinopathy (29%). Mean age of the patients with Type 2 diabetes (n = 347) was 60 ± 12 years, with a mean diabetes duration of
14 ± 9 years, the majority insulin-treated (84%) and the most frequently reported complications were erectile dysfunction in men (29%) and retinopathy (26%).

Table 1. Clinical characteristics of the study sample

<table>
<thead>
<tr>
<th>Total n = 627</th>
<th>Depressed CES-D ≥ 16 n = 202 (32%)</th>
<th>Non-depressed CES-D &lt; 16 n = 425 (68%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>314 (50)</td>
<td>110 (55)</td>
<td>204 (48)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53 ± 15</td>
<td>53 ± 14</td>
<td>53 ± 16</td>
</tr>
<tr>
<td>Married/partner</td>
<td>472 (75)</td>
<td>147 (73)</td>
<td>325 (77)</td>
</tr>
<tr>
<td>Native Dutch</td>
<td>564 (90)</td>
<td>174 (86)</td>
<td>390 (92)</td>
</tr>
<tr>
<td>Low education*</td>
<td>172 (27)</td>
<td>69 (34)</td>
<td>103 (24)</td>
</tr>
<tr>
<td>BMI</td>
<td>28 ± 6</td>
<td>29 ± 7</td>
<td>27 ± 5</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>347 (55)</td>
<td>125 (62)</td>
<td>222 (52)</td>
</tr>
<tr>
<td>Type 2 diabetes†</td>
<td>291 (84)</td>
<td>106 (86)</td>
<td>185 (84)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.0 ± 1.3%</td>
<td>8.0 ± 1.5%</td>
<td>7.6 ± 1.2%</td>
</tr>
<tr>
<td>Diabetes duration (years):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>22 ± 13</td>
<td>22 ± 12</td>
<td>22 ± 13</td>
</tr>
<tr>
<td>Type 2</td>
<td>14 ± 9</td>
<td>13 ± 8</td>
<td>14 ± 9</td>
</tr>
<tr>
<td>Diabetes complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinopathy</td>
<td>170 (27)</td>
<td>64 (32)</td>
<td>106 (25)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>76 (12)</td>
<td>42 (21)</td>
<td>34 (8)</td>
</tr>
<tr>
<td>Nephropathy§</td>
<td>62 (10)</td>
<td>24 (12)</td>
<td>38 (9)</td>
</tr>
<tr>
<td>Diabetic foot§</td>
<td>83 (13)</td>
<td>39 (20)</td>
<td>44 (11)</td>
</tr>
<tr>
<td>Erectile dysfunction**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-morbidity</td>
<td>134 (22)</td>
<td>46 (24)</td>
<td>88 (21)</td>
</tr>
<tr>
<td>Cardiovascular disease§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAID total</td>
<td>82 (13)</td>
<td>32 (16)</td>
<td>50 (12)</td>
</tr>
<tr>
<td>Depression treatment in past</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± SD or n (%). 
BMI, body mass index; CES-D, Centre for Epidemiologic Studies Depression Scale; HbA1c, glycated haemoglobin; NS, not significant; PAID, Problem Areas in Diabetes Scale; SD, standard deviation.

*Low education is defined as equal to/less than vocational training.
†n = 2 missing data; §n = 75 missing data; ¶n = 7 missing data; *n = 8 missing data; **n = 18 missing data.

Depressed patients significantly more often reported a lower education and a non-Dutch background relative to the non-depressed, which is in line with literature. The depressed also had a higher mean HbA1c (8.0 ± 1.5% vs. 7.6 ± 1.2%, P < 0.001), a greater prevalence of neuropathy (21 vs. 8%, P < 0.001) and a diabetic foot (20 vs. 11%, P = 0.002) and higher disease burden as expressed by higher reported diabetes-related distress (35 ± 20 vs. 13 ± 12, P < 0.001).

Depression, diabetes-related emotional distress and glycaemic control
The mean depression score (CES-D) in the study sample was 13 ± 11, with a higher score for Type 2 patients compared with Type 1 (14 ± 11 vs. 12 ± 11, P < 0.05). The means are below the cut-off of 16, but higher than found in the general Dutch population (8 ± 7). Based on their CES-D score (≥ 16), 32% (n = 202) could be classified as having elevated depression symptoms (hereafter referred to as 'depressed'), while 15% of the total sample (n = 93) reported elevated levels of diabetes-specific emotional distress (PAID ≥ 40), as shown in Table 2.
### Table 2. The association between depression symptoms, diabetes-related emotional distress and HbA1c and age, sex, type of diabetes and diabetes treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Depression CES-D ≥ 16</th>
<th>No depression CES-D &lt; 16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 202 (32%)</td>
<td>n = 425 (68%)</td>
</tr>
<tr>
<td></td>
<td>No elevated diabetes-related distress PAID</td>
<td>Elevated diabetes-related distress PAID</td>
</tr>
<tr>
<td>n</td>
<td>124 (19.8%)</td>
<td>78 (12.4%)</td>
</tr>
<tr>
<td>Age</td>
<td>54 ± 13</td>
<td>51 ± 15</td>
</tr>
<tr>
<td>Sex, female</td>
<td>55%</td>
<td>54%</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>64%</td>
<td>58%</td>
</tr>
<tr>
<td>CES-D</td>
<td>24 ± 7</td>
<td>28 ± 8</td>
</tr>
<tr>
<td>PAID</td>
<td>22 ± 10</td>
<td>56 ± 11</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.6 ± 1.1%</td>
<td>8.7 ± 1.7%</td>
</tr>
</tbody>
</table>

Data are mean ± sd or n (%).

CES-D, Centre for Epidemiologic Studies Depression Scale; HbA1c, glycated haemoglobin; NS, not significant; PAID, Problem Areas in Diabetes scale; sd, standard deviation.

Among the depressed, 39% (n = 78) reported concomitant elevated diabetes-specific emotional distress. PAID items that were most frequently endorsed by both Type 1 and Type 2 respondents as a serious problem were: concerns regarding complications, feelings of guilt about diabetes self-care and feeling overwhelmed by their diabetes. Type 1 and Type 2 patients did not significantly differ on level of HbA1c nor on diabetes-related distress. There were no significant differences in depression score, distress score or HbA1c level between Type 2 patients receiving only oral blood glucose-lowering medication, compared with those on insulin alone or on insulin combined with oral medication.

As a means to distinguish between poorer and better glycaemic control within our sample, we used the median HbA1c (7.6%). Contrasting both groups revealed that in the group with poorer control the percentage of patients who suffered from both depression and elevated diabetes-specific emotional distress was significantly higher than in the better-controlled group (19 vs. 7%, P < 0.001).

Age, sex and type of diabetes did not significantly differ between patients with poorer vs. better glycaemic control, defined as above and below the median.

**The mediating effect of distress in the relation between depression and glycaemic control**

In examining the mediating effect of distress, we found that (i) CES-D was significantly associated with HbA1c (B = 0.020, P < 0.001, with R² = 0.027); (ii) CES-D was significantly related to PAID (B = 1.094, P < 0.001, with R² = 0.393); (iii) PAID was significantly related to HbA1c (B = 0.016, P < 0.001, with R² = 0.050); and (iv) when adding PAID to the model in which CES-D is a predictor for HbA1c, CES-D loses its predictive value (B = 0.005, P = 0.428), while PAID explains the variance in HbA1c (B = 0.014, P < 0.001, with R² = 0.051), as shown in **Table 3**.

The Sobol test showed that the mediating effect of diabetes-distress in the relation between depression and HbA1c is statistically significant (Z = 5.14, P < 0.001). Age, sex, type of diabetes and body mass index were not significant covariates in any of the above-found relations.
Table 3. Results of linear regression testing the four hypotheses of the mediation model: (i) depression symptoms are significantly related to glycaemic control; (ii) depression symptoms are significantly related to diabetes-specific emotional distress; (iii) diabetes-specific emotional distress is significantly related to glycaemic control; and (iv) the relationship between depression symptoms and glycaemic control is significantly weakened when controlling for diabetes-specific emotional distress, in a sample of adult Type 1 and Type 2 diabetes patients in tertiary care.

<table>
<thead>
<tr>
<th>Complete study population (n = 627)</th>
<th>Coefficient (B)</th>
<th>95% CI</th>
<th>P-value</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) Depressive symptoms (CES-D), predicting glycaemic control (HbA₁c)</td>
<td>0.020</td>
<td>0.011 to 0.031</td>
<td>&lt; 0.001</td>
<td>0.027</td>
</tr>
<tr>
<td>(ii) Depression symptoms (CES-D), predicting diabetes-specific emotional distress (PAID)</td>
<td>1.094</td>
<td>0.987 to 1.201</td>
<td>&lt; 0.001</td>
<td>0.393</td>
</tr>
<tr>
<td>(iii) Diabetes-specific emotional distress (PAID), predicting glycaemic control (HbA₁c)</td>
<td>0.016</td>
<td>0.010 to 0.023</td>
<td>&lt; 0.001</td>
<td>0.050</td>
</tr>
<tr>
<td>(iv) Depression symptoms (CES-D), predicting HbA₁c, corrected for diabetes-specific emotional distress (PAID)</td>
<td>0.005</td>
<td>-0.007 to 0.017</td>
<td>&lt; 0.001</td>
<td>0.428</td>
</tr>
<tr>
<td>Diabetes-specific emotional distress (PAID), predicting glycaemic control (HbA₁c), corrected for depression symptoms (CES-D)</td>
<td>0.014</td>
<td>0.017</td>
<td>&lt; 0.001</td>
<td>0.051</td>
</tr>
</tbody>
</table>

CES-D, Centre for Epidemiologic Studies Depression Scale; CI, confidence interval; PAID, Problem Areas in Diabetes Scale; HbA₁c, glycated haemoglobin.

Post-hoc analysis: the odds for poor glycaemic control in subgroups of patients

When comparing glycaemic control across the four patient groups (neither depressed nor distressed; depressed only; distressed only; both depressed and distressed), those experiencing both depression and diabetes-distress showed significantly worse glycaemic control compared with the other three groups (87 ± 1.7% vs. 7.6 ± 1.2% in those without depressive symptoms; 7.6 ± 1.1% in depressed only and 7.7 ± 1.1% in the distressed only, P < 0.001), as represented in Table 2. Additional logistic regression analyses revealed that depression (CES-D ≥ 16) in the absence of diabetes-distress (PAID ≥ 40) did not elevate the risk of poorer glycaemic control (HbA₁c ≥ 7.6%, based on median of sample) [n = 124, odds ratio (OR) = 1.0, 95% confidence interval (CI) 0.7–1.5], nor did diabetes-distress in the absence of depression (n = 15, OR = 2.2, 95% CI 0.7–6.6). However, depression combined with diabetes-specific distress showed a three times higher odds ratio (n = 78, OR = 3.0, 95% CI 1.8–5.2) for suboptimal glycaemic control relative to the non-distressed, non-depressed group (n = 410).

Age, sex and type of diabetes were non-significant confounders in this relation. Choosing a higher cut-off score for poorer diabetes control (HbA₁c ≥ 8.5%) did not alter our findings.

Conclusions

The results from this relatively large cross-sectional sample of Type 1 and Type 2 diabetes outpatients from three different clinics confirmed our hypothesis that diabetes-distress partially mediates the relationship between depression and glycaemic control.

Notably, this relationship did not differ for both types of diabetes, suggesting the mediating role of diabetes-distress is independent of type of diabetes. However, we should keep in mind that the study was carried out in tertiary diabetes clinics, which made it likely that we included the more complex Type 2 diabetes patients.

We should be aware of the fact that, in our study, diabetes-distress accounted for only a small part of the variance in glycaemic control; the majority of those with higher HbA₁c values in our sample were neither depressed nor distressed. This points
to the importance of other determinants of poor diabetes outcomes besides depression and diabetes-distress, including educational, medical and social barriers.\textsuperscript{151}

Furthermore, we should keep in mind that depression symptoms and diabetes-specific emotional distress are two highly correlated constructs. Diabetes-specific emotional distress frequently occurs along with depression symptoms, which might indicate that those suffering from elevated diabetes-specific distress are in fact those with the highest depression scores. It might be that there is a tipping point as depression scores increase, where emotional well-being spills over into diabetes-related distress.

There are some limitations to our study. First, it was cross-sectional and we therefore cannot infer causal relationships. Second, we had complete data of approximately one third of the original sample and non-response may have caused selection bias. We did exclude patients with severe mental illness and depressed patients may have been less inclined to participate. While we lack information on the psychological status of the non-responders, rates of depression (depression symptoms) and the interactions found with diabetes-distress and glycaemic control are in concert with previous studies.\textsuperscript{52} 141 142 Our findings were based upon the self-reported symptoms of depression and cannot be generalized to diagnosed depressive disorders which would require a psychiatric interview.\textsuperscript{152} Our patient sample consisted of predominantly Caucasian, relatively highly educated diabetes patients. Confirmation of our results should be sought in prospective studies in more diverse patient populations. Regarding the measurement of blood glucose control, we relied on the most recent HbA\textsubscript{1c}. This is a valid measure of average blood glucose control, yet future studies could preferably incorporate more precise information on blood glucose variability, in particular hypoglycaemia and its association with mood and distress.

In this study, we observed that depression combined with high diabetes-specific distress showed a three times higher risk for elevated HbA\textsubscript{1c}. This combination presented in 12\% of the patients ($n = 78/627$). Our findings corroborate the recent study by Fisher \textit{et al}, who also found diabetes-distress to mediate the relationship between depression and glycaemic control in Type 2 diabetes patients, cross-sectional as well as longitudinal.\textsuperscript{140} This would suggest that, while depression and diabetes-distress are closely related constructs, our findings do underscore the importance of assessing both in clinical practice.\textsuperscript{153} A combination of a short depression screener such as the World Health Organization (WHO)-5\textsuperscript{154} with a five- or even one-item PAID,\textsuperscript{155} could serve as a rapid screening in order to detect those patients in which emotional distress is likely to jeopardize their glycaemic control.

With regard to depression treatment, our findings stress the importance of acknowledging and addressing diabetes-related issues in the context of depression treatment to help improve diabetes outcomes.\textsuperscript{74} 96 95 Indeed, diabetes-oriented group cognitive behaviour therapy in diabetes patients has been shown to significantly lower HbA\textsubscript{1c}.\textsuperscript{156 157}

In sum, our findings strongly suggest that diabetes-distress plays an important mediating role in the relationship between depression and poor glycaemic control, both for Type 1 and Type 2 diabetes. Addressing the emotional issues related to the experience of living with diabetes should therefore help to improve not only emotional well-being but also clinical outcomes.
CHAPTER 4

Development and reach of a web-based cognitive behavioural therapy programme to reduce symptoms of depression and diabetes-specific distress

Abstract

Objectives There is an urgent need for more effective and efficient depression treatments in diabetes. We developed a diabetes-specific version of the Dutch web-based ‘Coping with Depression’ (CWD) course. Here, we report on the development, reach, patients’ reasons for choosing our intervention and their characteristics.

Methods The CWD programme was amended for use in diabetes patients with co-morbid depression. Data were collected using a telephone interview, self-report questionnaires, and medical records.

Results Adding diabetes-specific topics to an effective web-based depression programme resulted in an 8-lesson intervention ("www.diabetergestemd.nl"), with minimal guidance by coaches. In the framework of a randomised trial, the intervention attracted serious interest of 540 patients. After screening, 255 depressed diabetes patients were enrolled. Less than half had a history of depression treatment; 80% reported the diabetes-specific approach to be an important reason for signing up.

Conclusion We successfully developed a diabetes-specific version of the web-based CWD course, which attracted a large group of patients. Our results affirm the importance of addressing diabetes-specific issues in the context of depression treatment.

Practice implications Our intervention could be implemented on a large scale at low costs, and may serve as a model on how to develop other illness-specific online self-help interventions.
Introduction

People with type 1 or type 2 diabetes can be seriously burdened by this chronic disease and its daily self-management, resulting in disease-related distress and reduced quality of life.\textsuperscript{158} Based on epidemiological research it is estimated that 20% of diabetes patients suffer from clinically relevant depression symptoms;\textsuperscript{52, 159} negatively impacting treatment adherence and diabetes outcomes.\textsuperscript{2, 160} Early recognition and treatment of depression in diabetes is therefore advocated.\textsuperscript{17, 139}

In clinical practice however, depression often remains untreated due to limited resources, lack of professional expertise and diabetes patients' reluctance to accept a referral to mental health care, among other factors.\textsuperscript{65, 117} Offering psychological help that clearly acknowledges disease-specific issues and helps patients cope more effectively with their diabetes could enhance attractiveness as well as treatment efficacy.\textsuperscript{94, 143, 161} Psychological and pharmacological therapies have shown to be effective in the treatment of depression in the general population.\textsuperscript{39} Cognitive behavioural therapy (CBT) is a well-established psychological treatment for depression that can be delivered face to face, in group sessions or as a self-help programme.\textsuperscript{46} With regard to the latter, Lewisohn's "Coping with Depression Course" (CWD) has a long tradition, and was made suitable for specific target populations, including adolescents, older adults and minority groups.\textsuperscript{48} The CWD course has also been adapted for patients with chronic diseases, addressing topics that apply to chronically ill patients with depressive symptoms.\textsuperscript{162}

Diabetes has been recognized as a psychologically demanding chronic illness.\textsuperscript{158} In addition to the 'adaptive tasks' related to being chronically ill,\textsuperscript{165} such as meeting medical requirements as prescribed, and seeking social support, people with diabetes are faced with disease-specific stresses, such as its demands of daily self-management and the risk of acute and long-term complications.\textsuperscript{28} In studies examining diabetes-specific emotional distress, issues that have been identified as particularly stressful are: (a) the life-long need to self-manage the diabetes 365 days a year by means of diet, exercise, self-monitoring and self-medication; (b) uncertainty around the interaction between emotional stress and blood glucose control; (c) the risk of disruptive blood glucose fluctuations (particularly hypoglycaemia) despite all efforts; (d) the risk of developing/further progression of invalidating complications; and (e) coping with unhelpful/negative social reactions and discrimination.\textsuperscript{95}

Most of above mentioned diabetes-specific issues were addressed in a 6-week CBT group programme, aimed at type 1 diabetes in poor glycaemic control,\textsuperscript{137} that showed to be well appreciated and effective in reducing diabetes distress.\textsuperscript{97} Interestingly, this programme was effective in improving glycaemic control in patients with elevated depressive symptoms.\textsuperscript{157}

Given the scope of the problem of depression in diabetes, there is an urgent need to seek ways to enhance reach. Recent advances in e-mental health hold promise for effective interventions delivered through the Internet at low costs with positive results.\textsuperscript{151-164} Importantly, e-mental health to a large extent overcomes the barriers of the traditionally segmented health care system. In diabetes care, administering interventions via the Internet may be particularly beneficial in improving reach and overcoming logistical and financial barriers both on the part of health care providers as patients.\textsuperscript{165, 166}

Two web-based versions of the CWD intervention ("Colour Your Life") have been developed in Dutch and appeared to be effective in reducing symptoms of depression.\textsuperscript{57, 167} Controlled studies have shown that delivering the CWD program via the Internet is feasible and cost-effective, potentially reaching a large number of patients. The online versions of the CWD focus on acquiring six basic skills: pleasant activity scheduling, cognitive restructuring, relaxation, communication, coping with
worries, and assertiveness. Relaxation is known to have beneficial effects on depression and positively impact blood glucose control in type 2 diabetic patients. In depressed patients, social skills training has shown to decrease social anxiety, establish self-confidence, and improve social interaction abilities. A large body of research suggests that social support can enhance adaptation to diabetes, e.g. by learning how to cope with negative social reactions on diabetes, avoiding conflicts, stress and isolation from family and friends. Furthermore, homework assignments are considered a core component of CBT, improving treatment efficacy. It has been stressed more than once that minimal therapist support (coaching) is needed for Internet therapy to be effective, by improving compliance with the course, and quality of treatment.

We have developed a web-based self-help intervention, specifically suited for diabetes patients. Here, we report on this development of the intervention and its reach.

**Methods**

**Development of the diabetes-specific depression intervention**

We considered the online “Coping with depression course” (CWD) ([www.kleureleven.nl](http://www.kleureleven.nl)) a good basis for developing a diabetes-specific depression intervention, and probably most effective when offered with minimal guidance or coaching. We added the diabetes-specific topics via a structured procedure, involving diabetes patients and (mental) health care providers. First, we consulted a panel of five diabetes patients recruited via the Dutch diabetes patient association. One of the patients was female, age range was 40–78 years, three patients had type 1 diabetes, and two had type 2 diabetes; diabetes duration varied from 12 to 50 years. Patients individually reviewed the online CWD course and advised us on elements that were considered inappropriate, in need of improvement or missing. Facilitation of readability for those suffering from impaired sight was advised, by adding more contrasts to colour of letters and background, and by enlarging font size. General suggestions for improvement were: motivate patients to stay in the course; add interaction with therapist; and favour the attractiveness of patient videos.

The next step was to identify key issues related to coping with diabetes derived from our cognitive behavioural therapy (CBT) group programme for type 1 diabetes patients, and relevant for the new programme: (1) the cognitive behavioural model of diabetes; (2) stress and diabetes; (3) ‘living with the future’ (worries about complications); and (4) diabetes in social relationships. After having developed the new intervention, we again consulted our patient panel. We also consulted a diabetes nurse practitioner, a dietician, and a medical psychologist, who were unanimously positive about the intervention.

**Studying the effectiveness of the intervention: eligibility and recruitment**

To examine the effectiveness of our intervention, it was administered within the framework of a randomised controlled trial. All information on the study was provided via a freely accessible website ([www.diabetegestem.nl](http://www.diabetegestem.nl)), and patients could sign up from July 2008 until August 2009. During this period, the study was advertised several times through different media in the Netherlands and Belgium, including diabetes patient and professional journals, newspapers, and on various websites.

Adult diabetes patients with co-morbid symptoms of depression (defined as CES-D score ≥16), could sign up for participation in our study via the website, without needing a referral. Patients with reading problems (due to insufficient Dutch language skills, visual impairments, illiteracy) or without Internet skills or an e-mail address were excluded. Other criteria for exclusion were: a history of suicide attempt(s), current suicidal ideation, bipolar depression, psychotic disorder, pregnancy and recent
loss of a significant other. Furthermore, patients had to agree with us contacting their treating physician to inform him/her about the patient’s participation in our study and to collect data on glycaemic control (HbA1c). Exclusion criteria were clearly mentioned on our website, and patients could fill out a form indicating the reason for having to exclude themselves. It was clearly mentioned that during the study, patients were allowed to use any additional mental health care at their own discretion.

The number of visitors of our study website was registered, and used to estimate the level of interest. All patients were asked to indicate their reason for choosing particularly our intervention, and whether they had previously sought help for their depression.

Measures

Socio-demographics and clinical characteristics

These were self-reported as a part of online assessment: socio-demographic data (age, gender, marital status, highest level of completed education, and current occupation), depression profile (depression treatment in past, currently taking anti-depressive medication), and diabetes profile (type of diabetes, duration, treatment regimen, and complications). Glycaemic control (HbA1c) was retrieved from patients’ medical charts via their treating physician.

Depression

Symptoms of depression were assessed with the Dutch validated version of the Centre for Epidemiological Studies Depression scale (CES-D). The CES-D is a self-report screening instrument which measures the frequency with which participants have experienced specific symptoms of depression within the preceding week. The questionnaire contains 20-items with a 4 point Likert scale. The total score can range from 0 to 60, where higher scores indicate greater frequency of depression symptoms. A cut-off score of 16 or higher is generally accepted as indicative of clinical depression.146 147

To diagnose depression, the Dutch World Health Organization Composite International Diagnostic Interview (CIDI) was used. The CIDI is a fully structured diagnostic interview which assesses diagnostic criteria of mental disorders according to the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV).147 In our study, we administered the CIDI-auto, a computerised version of the CIDI, and qualified substitution of the face-to-face interview,178 per telephone. Interviewers were master students in Clinical Psychology who received a half day of training by a professional. Since questions and routes are fully specified, no clinical judgement is required. The following sections of the CIDI were administered: section D: anxiety disorders; section E: depression; section F: bipolar disorder; and section G: psychotic disorder.

Diabetes-specific emotional distress (PAID)

Diabetes-specific emotional distress was measured using the Dutch validated Problem Areas in Diabetes Scale (PAID), a 20-item self-report questionnaire. Items are rated on a 5 point Likert scale, ranging from 0 ("not a problem") to 4 ("a serious problem") and sum scores are converted to a 0–100 scale by multiplying scores with 1.25. The commonly used cut-off score of ≥40 was used to indicate elevated levels of diabetes-specific emotional distress.24

Statistical analyses

SPSS 15.0 was used to carry out statistical analyses. Baseline characteristics of participants in our study were compared for several subgroups, using Students t-test,
\( \chi^2 \) tests and Fisher's exact test (in case of no normal distribution). Two-sided tests with the level of significance established at 0.05 were applied for all analyses.

**Results**

The diabetes-specific depression intervention

We synthesized all the information gathered from research and the patient panel, and included diabetes-specific topics in the eight scheduled lessons of the online 'Coping with depression' (CWD) course. A summary of the content of the new, diabetes-specific depression intervention is presented in Table 1. The online programme was developed in close collaboration with the developers of the web-based CWD course of 2004, Heleen Ripper and Jeanette Kramer of ICOM, part of the Trimbos Institute, and an ICT company. The development phase, including text writing, script writing, video-taking and editing, took about 12 months.

<table>
<thead>
<tr>
<th>Lesson</th>
<th>Topic in generic web-based depression CBT</th>
<th>Diabetes-specific topic added</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Introduction to the course.</td>
<td>Association diabetes and depression. Positive and negative spiral in diabetes.</td>
</tr>
<tr>
<td></td>
<td>Cognitions, behaviour and emotions are associated. Purpose of the course is to change a 'negative spiral' into a positive spiral.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Pleasant activities.</td>
<td>Demands of daily self-management</td>
</tr>
<tr>
<td></td>
<td>Recognizing automatic thoughts.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Physical activity.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thinking mistakes.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Non-helpful cognitions and pleasant activities.</td>
<td>Worrying about diabetes-specific complications.</td>
</tr>
<tr>
<td>5</td>
<td>Anti-ruminating techniques</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Assertiveness</td>
<td>Asking/declining help Coping with reactions from environment on diabetes</td>
</tr>
<tr>
<td>7</td>
<td>Communicating</td>
<td>Communicating about diabetes in general Communicating with health care professionals</td>
</tr>
<tr>
<td>8</td>
<td>Relapse prevention</td>
<td></td>
</tr>
</tbody>
</table>

Similar to the CWD course, the new intervention focuses on six skills, which are addressed in eight consecutive lessons: pleasant activity scheduling, cognitive restructuring, relaxation, communication, coping with worries, and assertiveness. Next to the six skills, the importance of "rewarding yourself" is underscored, and repeatedly advised as part of the eight lessons.
Each lesson is divided into four sections. First, a short introduction, in which the topic of that particular lesson is introduced, and the core information of the previous lesson is repeated. Second, new information is provided. After this, the homework assignments are explained. Finally, the lesson is summarized and evaluated.

Patients are advised to go through one lesson and send in their homework assignments each week. We included minimal guidance, which existed of "coaches", in our case psychologists with training in CBT, providing patients with (e-mail) feedback on their homework assignments. Coaches received a half of a day instruction on the web-based programme and the feedback protocol. Feedback is provided within 3 working days and formulated in a positive, constructive tone. It mainly focuses on the cognitive restructuring principles and applying the new-learned skills in daily life.

Since reminders have shown beneficial in the effects in depression interventions,179 we chose to send standardised e-mail reminders, when a patient fails to send in homework within one week. After two weeks, a second reminder is send, mentioning that when not having sent homework within another week, the patient is considered no longer interested in completing the course, and therefore to have dropped out.

Each lesson contains short videos of example patients. The three example patients live with diabetes and struggle with depression symptoms: one middle-aged overweight woman with type 2 diabetes, one younger woman with type 1 diabetes planning pregnancy, and one middle-aged man with type 2 diabetes and erectile dysfunction. The patients explain their problem, how they exercise the skills which are taught in the course, and their benefits in daily life (Figure 1).

![Figure 1](image)

**Figure 1.** Screenshot of a lesson in the web-based, diabetes-specific depression course

During the course, patients can daily self-monitor their mood, and determine which events either improve or worsen their mood. It is suggested to relate these findings with blood glucose readings from self-tests, to explore a possible link between mood and blood glucose control. Since the intervention is not accompanied by a text
book, an online library gives patients the opportunity to print out all texts of the course, thus creating their own reference book. A discussion forum, offers patients the opportunity to chat with other patients.

**Reach**

During the inclusion period the website had approximately 5000 unique visitors. In total 340 visitors expressed serious interest in participation in our study. Forty percent of the patients interested in participation (N = 215) were not eligible due to exclusion criteria. Interestingly, 7% of those interested in participation (n = 37) did not have elevated depression symptoms as measured by the CES-D (>15). Finally 255 patients (47%) of all interested were included in the randomised controlled trial.

The majority of our study population was self-referred. Only a handful of patients found our intervention via their treating physician or diabetes nurse practitioner.

**Characteristics participants**

Participants’ baseline socio-demographic, clinical and psychological characteristics are presented in Table 2. Mean age of our study sample (N = 255) was 50 ± 12 years, with over half being female (N = 155, 61%). Most were Caucasian (N = 227, 89%), married or had a partner (N = 199, 78%), and only a minority of the patients had lower education (N = 40, 10%), while a third of our sample was employed (N = 83, 33%). About half of our study population had type 2 diabetes (N = 141, 55%). The overall mean diabetes duration was 14 ± 12 years.

Mean score on the CES-D was 28 ± 7. More than half of our sample reached the criterion for a diagnosis of major depressive disorder (MDD) (N = 146, 57%), of which the majority had an onset longer than one year ago (N = 133, 91%). More than a third of our sample was diagnosed with an anxiety disorder (N = 95, 37%). Mean score on the PAID was 40 ± 19, with 50% indicating seriously elevated diabetes distress, based on PAID cut-off of 40 and higher (N = 127, 50%).

About half of our study population, (47%, N = 120) had received depression treatment in the past. Those who received depression treatment in the past did not have higher mean depression symptoms (CES-D) compared to those with no previous depression treatment, but were diagnosed with MDD on the CIDI diagnostic interview more frequently (65% vs. 50%, \( \chi^2 = 6.0 \) (1), \( p = 0.016 \), and had a earlier onset age of depression (34 years ± 14 vs. 41 years ± 16, \( p = 0.006 \). No differences were found between the groups regarding their diabetes profile, or level of diabetes-specific distress, nor did they differ in their opinion regarding the importance of our intervention being diabetes-oriented and offered via the Internet.

**Reasons for choosing a web-based diabetes-specific depression intervention**

When asked for the main reason[s] for choosing our intervention, 80% of the patients confirmed that the diabetes-oriented approach to depression was considered important. This group showed higher diabetes-specific emotional distress scores (41 ± 19 vs. 31 ± 17, \( p = 0.015 \) than the other twenty percent, but depression scores were not different. Seventy-one percent agreed to the advantage that the intervention could be followed from home, and 65% that it offered flexibility as to the time engaging in the programme.
Development and Reach

2.

Discussion and conclusion

Discussion

We are the first to have developed a diabetes-specific web-based, guided self-help depression intervention. The potential need for such an intervention originates from studies on generic depression treatment in diabetes patients, in which the authors advise to address diabetes-specific emotional problems in depression treatment. Furthermore, the number of people with diabetes around the world is growing fast, and approximately twenty percent of them are suffering from clinically relevant depression symptoms. Many of them do not appear to receive adequate mental health care, resulting in unnecessary suffering and negative health outcomes. This indicates the magnitude of the specific group which our intervention is aimed at.

We succeeded in integrating diabetes-specific issues while staying in the mainframe of the CWD course and without adding extra lessons. Acknowledging the stresses of living with diabetes and offering effective coping strategies should help to increase the attractiveness of the programme and make patients feel understood. While the efficacy of our intervention is yet to be demonstrated, data on reach indicate that the intervention is indeed attractive to a large group of diabetes patients with comorbid depression, many of whom also report high diabetes-specific emotional distress.

Table 2. Participants’ socio-demographic, clinical and psychological characteristics at baseline.

<table>
<thead>
<tr>
<th>Total, ( n = 255 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Socio-demographics</td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Caucasian</td>
</tr>
<tr>
<td>Marital state – with partner</td>
</tr>
<tr>
<td>Education</td>
</tr>
<tr>
<td>Lower</td>
</tr>
<tr>
<td>Middle</td>
</tr>
<tr>
<td>Higher</td>
</tr>
<tr>
<td>Employed</td>
</tr>
<tr>
<td>Diabetes profile</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Insulin-treated Type 2</td>
</tr>
<tr>
<td>HbA1c level, %</td>
</tr>
<tr>
<td>Duration of diabetes, y</td>
</tr>
<tr>
<td>1 or more diabetes complications</td>
</tr>
<tr>
<td>Psychological profile</td>
</tr>
<tr>
<td>Depression symptoms (CES-D score, range 16–60)</td>
</tr>
<tr>
<td>Diagnosed with MDD (WHO CIDII)</td>
</tr>
<tr>
<td>History of professional depression treatment</td>
</tr>
<tr>
<td>Diabetes-specific emotional distress (PAID score, range 0–100)</td>
</tr>
<tr>
<td>Elevated diabetes-specific emotional distress (PAID ≥40)</td>
</tr>
</tbody>
</table>

Values are presented in No (%) or mean ± SD.

Abbreviations: CES-D, Centre for Epidemiological Studies Depression Scale; PAID, Problem Areas In Diabetes Scale; CIDII: World Health Organisation Composite International Diagnostic Interview; MDD, Major Depressive Disorder; HbA1c, glycosylated hemoglobin

*Lower education = primary education or lower general secondary education; middle = intermediate vocational education or high school; high = higher vocational.
Either way, with approximately 150,000 Dutch diabetes patients with elevated depression symptoms,100 and an estimated annual 4320 visitors,101 this would mean that we reached about three to four percent of our target population. Of course, we need to appreciate the fact that our intervention was the first of its kind to be delivered via the Internet, in the context of a trial. Growing acquaintance with our intervention, raising public awareness of the frequent co-occurrence of depression in diabetes, and embedding our intervention in routine care is likely to enhance reach and thereby it is social impact. Indeed, we saw an elevated interest in our study as a direct result of each publicity effort.

We reached a substantial subgroup of diabetes patients who had not received professional mental health care before, suggesting our intervention could lower the threshold and reach a new audience. Most patients found our website through patient magazines, and only a minority was referred by health care professionals. We can assume that increasing awareness and acceptance of web-based interventions among health care professionals, both diabetologists and mental health care professionals, will enhance the uptake and dissemination.

Our sample showed a majority of women (61%), in accordance with depression presenting two times more often than in males, and women more frequently seeking mental health care.102 The study sample was relatively young, mainly Caucasian, and with relatively high education levels. It might be that we included the highly motivated and well-controlled patients, who have a special interest in their diabetes and who take their self-management tasks highly serious. Based on the characteristics of the Dutch diabetes patient population, we could have expected more type 2 patients, elderly patients, non-Caucasians and patients with lower education.103 Relatively low Internet literacy in these groups may explain under representation in our study, but is likely to change in the coming years with increasing availability of Internet services and e-health applications on a larger scale.104

Although the web-based character of our intervention has the potential to have high reach since it surpasses certain time-, place- and personal barriers, we do acknowledge that our intervention will not be eligible for all diabetes patients suffering from emotional distress. For instance patients who are incompetent using the computer and Internet, those who prefer a face-to-face treatment and perhaps patients who are too severely depressed require an alternative approach. A planned study on the predictors of the effectiveness of the web-based intervention is believed to shed more light on the suitability of our intervention for certain subgroups of patients.

Drop-out is a well-known problem in the treatment of depressed patients in general. A recent implementation study of a generic web-based depression intervention in primary care showed, that adherence in the web-based depression intervention was slightly higher (36%) than in treatment as usual condition, in this case being 4–5 treatment session with a general practitioner optionally combined with antidepressant medication (34%).105 Future studies are needed to examine strategies that can reduce treatment drop-out.

**Conclusion**

Depression presents as a major problem in people with diabetes, but often remains unrecognised and untreated. Offering online self-help can potentially reach a large group of patients that otherwise would stay deprived of adequate mental health care. We developed a diabetes-specific version of the online Coping with Depression course with minimal guidance that proved to be attractive to both type 1 and type 2 diabetes patients with co-morbid depression. Half of the participants suffered from diabetes-specific emotional distress, known to be associated with motivational problems and poor diabetes self-care. Addressing both depression and diabetes distress may
therefore help to promote emotional well-being, and facilitate adequate diabetes self-management and thus improve subsequent health outcomes.

Practice implications
Our web-based intervention provides a new treatment option for people with diabetes and co-morbid depression. The web-based character of the intervention omits obstacles of time, place, and distance, thus having the potential for dissemination to a large number of patients across settings and countries. Once developed, the programme can be delivered at relatively low costs, as a stand alone or as part of a health care programme, with or without guidance. Reimbursement issues from insurance companies, related to the patient’s anonymity, may arise, but in principle should not stand in the way of further integration and adoption. For the purpose of international dissemination, linguistic and cultural adaptations of the programme are needed and planned.

Future research should clarify if offering our intervention to patients with mild depressive symptoms can help to empower them and prevent major depression and future depressive episodes. It should also help us ascertain cost-effectiveness. It certainly would seem fit to use the programme as a prevention tool for diabetes patients interested in preserving and promoting their mental fitness, thereby reducing the risk of developing mental health problems in the future.

Tailoring an effective web-based (self-help) programme to the needs of specific somatic patient groups is a concept with relevance not only to diabetes but to other chronic medical conditions, e.g. COPD, arthritis and heart failure. Our programme may therefore serve as an example for other chronic illnesses, where psychological distress is found to be common.

Results of our RCT will inform us on the effectiveness of the intervention, differential effects and ways of improving compliance and outcomes.
CHAPTER 5

Web-based depression treatment for Type 1 and Type 2 diabetic patients: A randomized, controlled trial

Abstract

Objective Comorbid depression is common in patients with type 1 and type 2 diabetes, adversely affecting quality of life, diabetes outcomes and mortality. Depression can be effectively treated with Cognitive Behavior Therapy (CBT). Internet is a new and attractive method for delivering such an intervention on a large scale at relatively low costs. This study evaluates the effectiveness of web-based CBT for depression treatment in adults with type 1 or type 2 diabetes, with minimal guidance.

Research design and methods A randomized, controlled trial was conducted in 255 adult diabetes patients with elevated depressive symptoms, in the Netherlands. Outcomes were depressive symptoms (primary outcome), diabetes-specific emotional distress and glycemic control (secondary outcomes). Assessments were at baseline, post-treatment, and at 1 month follow-up.

Results The web-based CBT was effective in reducing depressive symptoms (with intention-to-treat analyses: \( P = 0.04, d = 0.29 \) and clinical improvement 41% vs. 24% \( P < 0.001 \); and per protocol analyses \( P < 0.001, d = 0.70, 56\% \) vs. 24% \( P < 0.001 \)). Additionally, the intervention reduced diabetes-specific emotional distress \( (P = 0.05) \). We found no beneficial effect of the intervention on glycemic control \( (P > 0.05) \).

Conclusions Web-based CBT depression treatment is effective in reducing depressive symptoms in adults with type 1 and type 2 diabetes patients. Additionally, the intervention reduces diabetes-specific emotional distress in depressed patients.
Introduction

Affecting 10 to 20% percent of adult diabetic patients, depression is a common co-morbid health problem among people with type 1 or type 2 diabetes. Comorbid depression in diabetes results in a lower quality of life, poorer glycemic control, an increased risk of developing diabetes-related complications, and higher mortality rates. Depression, therefore, needs to be regarded a serious and common comorbidity in diabetes, negatively affecting both mental and physical health.

In routine diabetes care, depression remains untreated in at least 50% of the patients. Undertreatment occurs partly because patients are not inclined to discuss their emotional problems with their physician, and health care professionals feel under-resourced and lack the tools to refer or treat depression in their diabetic patients.

A recent meta-analysis showed that depression in people with diabetes can be treated effectively with antidepressant medication, psychotherapy or combined therapy, with possible benefits on diabetes outcomes. A meta-analysis showed that using the Internet to deliver psychotherapy is an effective treatment option for depression and could help to increase reach and facilitate access to effective depression treatment against relatively low costs. Lewinsohn’s Coping with Depression course (CWD) is currently the most studied and proven effective cognitive behavioral therapy (CBT) treatment of depression, and given its highly structured character, is suitable for making a Web-based version. The effectiveness of a Web-based version of CWD -Color your Life (CYL)- has been shown. Because CWD, and specifically CYL, is highly structured, it requires adaptation to subgroups of patients that are being addressed, such as those previously developed and tested in randomized controlled trials in elderly, young people, and patients with chronic diseases. Between 56 and 75% of depressed patients with diabetes experience high levels of emotional distress directly related to diabetes. Recent studies have shown that the beneficial effects of depression treatment on glycemic control are mediated by diabetes-related distress. Health-care providers have therefore been advised to address disease-specific emotional distress to improve the effectiveness of depression treatment, and to benefit diabetes outcomes. Therefore, in close collaboration with the researchers who developed CYL, we adapted this course to meet the needs of diabetic patients, thus maximizing acceptability. This diabetes-sensitive CYL (Diabetesteremdel, DG.nl) takes into account the specific coping issues diabetic patients are faced with related to physical problems, the daily burden of self-management and the risk of long-term complications. The need to adapt CWD to diabetic patients was confirmed by consulting diabetic patients, professionals, and from our own clinical experience.

The primary aim of this study was to test the effectiveness of DG.nl in a randomized controlled trial. We hypothesized that depressive symptoms would reduce significantly more in the intervention condition than in the control condition. Additionally, we expected beneficial effects of the intervention on diabetes-specific emotional distress and glycemic control.

Research design and methods

The study was approved by the Medical Ethics Committee of the VU University Medical Center.

Design overview

The effectiveness of the intervention was tested in a randomized controlled trial, and its design is described in more detail elsewhere. Eligible patients were randomly assigned to the Web-based intervention or to a 12-week waiting list control group. The
assessments in the intervention group were scheduled directly after participants completed or had stopped the Web-based intervention (postassessment), and at a 1 month follow-up assessment (see flow chart, Figure 1).

Setting and Participants
Patients were recruited from July 2008 through September 2009 by advertisements in various general and diabetes-specific media. Patients could individually sign up for participation in the study through an open access study Web site. After having signed informed consent, patients were invited to fill out the baseline assessment through a personal online questionnaire, and they received a telephone administered diagnostic interview. To participate in the study, adult diabetic patients were required to have a score of ≥16 on the Centre for Epidemiological Studies Depression scale (CES-D), have an e-mail address and access to the Internet. Exclusion criteria were a history of suicide attempt(s) or current suicidal ideation, bipolar depression or psychotic disorder, pregnancy, and recent loss of a significant other (<6 months ago).

Randomization
Randomization by computer was used to assign participants to the experimental or control condition, at individual level. Subjects were informed about the outcome of randomization by e-mail, directly after the diagnostic interview. Blinding of participants was not possible given the nature of the study. The coaches were blinded to whether patients were allocated directly to the intervention or gained access to the intervention at a later stage, after the waitlist phase.

Interventions
Web-based Cognitive Behavioral Therapy
A detailed description of the intervention can be found elsewhere. In short, participants individually went through eight consecutive lessons that provided written and spoken information and videos of depressed diabetes patients explaining how they learned from the course. Coaches (certified health psychologists) provided feedback on homework assignments ≤3 working days. Feedback was to a large degree standardized and consisted of a concise, constructive reply on the CBT techniques, meant to help patients understand and apply the CBT skills in daily practice. In case homework was not received, patients were sent reminders after 1 week and after 2 weeks. If no reply was received ≤3 weeks, participants received an e-mail stating we had to assume that they were no longer interested in the intervention, and were invited to fill out the postmeasurement. However, if still interested, they were invited to re-enter the course.

Waiting-list
Participants allocated to the waiting list control group completed measurements 8 weeks (post-assessment) and 12 weeks after randomization (1-month follow-up assessment). After this 12-week waiting period, patients received a password that allowed them to log in to the web-based intervention, if they still had elevated depressive symptoms (CES-D ≥ 16).
RCT

CHAPTER 5

Assessed for eligibility (n = 410)

Excluded (n = 155)
Not meeting the inclusion criteria (n = 139)
Refused to participate (n = 16)

Randomized (n = 255)

Allocated to intervention (n = 255)
Completed whole eight-lesson intervention (n = 53)
Loss to follow-up (n = 52)
Completed follow-up (n = 73)

Allocated to waiting list (n = 130)
Loss to follow-up (n = 36)
Completed follow-up (n = 94)

Included in one-month follow-up intention to treat analyses (n = 125)*

Included in one-month follow-up intention to treat analyses (n = 130)*

* All randomized cases were analyzed, using the Multiple Imputation for missing data method.

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) Flow Diagram

Measurements

Baseline measures

Characteristics of the study sample were self-reported as part of the online baseline assessment: sociodemographic data (age, gender, marital state, level of education, and current occupation), lifestyle (smoking, alcohol use), and data on diabetes (type of diabetes, treatment regimen, and diabetes duration and diabetes complications), BMI and use of antidepressant medication.

The World Health Organization Composite International Diagnostic Interview – auto (WHO CIDI-auto) was used to diagnose depression and to exclude patients when detecting bipolar disorder, psychotic features, current suicidal ideation or suicide attempt(s) in the past. The WHO CIDI-auto is a computerized, fully structured diagnostic interview that assesses diagnostic criteria of mental disorders according to the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV). 16th Questions and routes are fully specified, no clinical judgment is required. Interviewers were master students in clinical psychology at the VU University in Amsterdam, trained in the administration of the WHO CIDI-auto by telephone. At the end of the telephone interview, standardized feedback was given to the patient on the outcome.

Outcomes

The main outcome was symptoms of depression, assessed with the CES-D, a widely-used 20-item self-report instrument. The CES-D has shown strong criterion validity compared with structured diagnostic interviews. 16th Respondents are asked to indicate the frequency with which they experienced depressive symptoms in the preceding week. Scores range from 0 to 60, with scores of ≥16 representing a clinically significant level of depressive symptoms.

Secondary outcomes were diabetes-specific emotional distress and glycemic control. Diabetes-specific emotional distress was assessed with the Dutch version of the Problem Areas in Diabetes (PAID) scale, a widely used 20-item self-report questionnaire. 24th Items pertain to negative emotions related to living with diabetes,
rated on a 5-point Likert scale, ranging from 0 ("not a problem") to 4 ("a serious problem"). Sum scores are converted to a 0-100 scale. We used a score of ≥ 40 as cutoff for high distress. 24-89

As an indicator of glycemic control, patients’ glycosylated hemoglobin (AIC, reference range 4.3-6.1%) measured closest to the date of premeasurement and the 1-month follow-up was retrieved from their treating physicians. Poor glycemic control was defined as AIC of ≥ 8%. 187

Sample size calculation
The sample size was calculated based on the expected difference in depressive symptoms, which was the primary outcome variable. Based on a statistical power of 0.80, with an alpha of 0.05, 100 subjects were required in each group to be able to detect differences with an effect size of 0.35. 126 With an expected 30% study attrition, we determined the study sample size needed randomization of 286 participants.

Statistical analysis
Statistical analyses were completed with SPSS 15.0 and Stata 10.0 software. Baseline characteristics were compared for the intervention and control group using Student t tests, χ²-tests, and analyses of variance to test whether randomization had been successful. Two-sided tests with the level of significance established at 0.05 were applied for all analyses.

Analyses were performed on both intention-to-treat (ITT) principles and per-protocol (PP) analyses. In PP analyses, subjects who completed the full eight lessons of DGl were compared with the control group.

Longitudinal regression analyses were performed using generalized estimating equations. Interaction effects of treatment (intervention versus control group) X time (baseline, postassessment, and at 1-month follow-up) were calculated to test whether developments over time between intervention and control group differed. Because variability was expected in the duration of the course (considering our rules for dropping out of the course, the duration of the course could vary between 5 and 24 weeks), we corrected for time between pre- and posttreatment measurement in all analyses. Furthermore, all analyses were corrected for baseline depressive symptoms and for use of self-reported pharmacologic and psychologic treatment during the study.

Between-group effect sizes were calculated using Cohen d, using the following formula: 
\[ d = \frac{M_1 - M_2}{\sigma_{pooled}} \]

in which \( \sigma_{pooled} \equiv \sqrt{(\sigma_1^2 + \sigma_2^2) / 2} \). Effect sizes larger than \( d \geq 0.8 \) are considered to be large, \( d = 0.5 - 0.8 \) as moderate, and \( d = 0.2 - 0.5 \) as small. 124

In addition, clinically significant change was determined, defined as having recovered and showing significant improvement on the CES-D. Recovery was defined as having a score <16 on the CES-D. 146 Improvement was determined following the suggestions of Jacobson and Truax, 188 calculating a reliable change index (RC) using the following formula:
\[ RC = \frac{x^2 + 1}{\text{diff}^2} \]

Patients who both improved and recovered were considered as being "clinically significant improved."

Learning from previous studies on web-based interventions, we expected high study attrition rates. 189 Nonrandom study attrition may jeopardize ITT principles and lead toward an overestimation of effect sizes. Therefore, when establishing nonrandom study attrition, missing data are imputed, using multiple imputation by chained equations. In contrast to other imputation techniques, this method minimally alters variance of data, thus providing the best estimates of missing data, at least until 50% of missing data. 189 Consequently, all analyses could be performed on complete data.
Results
Randomization and study attrition
Of the 410 individuals who expressed interest in our study, 255 patients were eligible and randomized: 125 patients were allocated to the intervention group, and 130 to the control group. Study attrition for the full study sample was 82 (32%) for postassessment, 88 (35%) for the 1-month follow-up assessment, and was higher in the intervention group than in the control group: 52 (42%) vs. 36 (28%; P = 0.01). Study dropouts were more often diagnosed with an anxiety disorder [49% vs. 31%, P < 0.01]. Within the control group, study dropouts showed higher baseline depression scores of 31 ± 8 vs. 27 ± 7 for non-dropouts (P < 0.01; Figure 1).

Regarding the intervention group, study attrition was higher in non-completers of the course at 1-month follow-up (45 of 72, 63%) than in completers of the course (7 of 53, 13%; P < 0.001). Because study attrition was higher in the intervention group (specifically in non-completers of the course) relative to the control group, study attrition was not completely at random, justifying multiple imputation.189

Baseline characteristics
Baseline sociodemographic and clinical characteristics of the study sample are presented in Table 1. The intervention and control groups did not significantly differ regarding demographic and clinical characteristics at baseline. The study sample was 89% white (n = 227), 61% female (n = 155), 97% were moderately to highly educated (n = 247), and 55% (n = 141) were diagnosed with type 2 diabetes. High levels of depressive symptoms were confirmed at baseline, with a mean CES-D score of 28 ± 7. Diabetes-specific emotional distress was also high, with a mean PAID score of 40 ± 19. Mean $A_1$ was 7.4% ± 1.3%, indicating relatively well-controlled diabetes, with 27% having an elevated level of $A_1$ (> 8.0%). Seventy-nine patients (31%) self-reported one or more diabetes complication.

Change in depressive symptoms
Mean time between pre-and post-treatment was 12 ± 8 weeks for the intervention group, comprising 14 ± 9 weeks in course completers and 11 ± 7 weeks in course non-completers. Generalized estimating equation analyses revealed a significant treatment by time interaction effect on depressive symptoms (CES-D; P < 0.001). For depressive symptoms at 1-month follow up, $d = 0.29$ (95% CI 0.17 – 0.40).

Secondary outcomes
A significant treatment times time effect was found for PAID (P < 0.001). No significant treatment effect was found for $A_1$-levels (P > 0.05). When patients with elevated baseline $A_1$-levels only were examined, a significant treatment effect was still not found for $A_1$ (P > 0.05).

Clinically significant improvement
Compared with the control group, a significantly higher percentage of the intervention group showed clinically significant improvement at postassessment (37% vs. 19%, P < 0.001) and at the 1-month follow-up (41% vs. 24%, P < 0.001).
Table 1. Baseline socio-demographic and clinical characteristics of participants at baseline.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n = 255)</th>
<th>CBT participants (n = 125)</th>
<th>Waiting list Control participants* (n = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Socio-demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, y</td>
<td>50 ± 12</td>
<td>48 ± 12</td>
<td>51 ± 12</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>155 (61)</td>
<td>82 (66)</td>
<td>73 (56)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>227 (89)</td>
<td>110 (88)</td>
<td>117 (90)</td>
</tr>
<tr>
<td>Marital state – with partner, n (%)</td>
<td>199 (78)</td>
<td>99 (79)</td>
<td>100 (77)</td>
</tr>
<tr>
<td>Education level, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No formal qualifications</td>
<td>8 (4)</td>
<td>5 (5)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>High school or lower / middle vocational qualifications</td>
<td>136 (53)</td>
<td>70 (56)</td>
<td>66 (51)</td>
</tr>
<tr>
<td>College qualifications or more</td>
<td>111 (44)</td>
<td>50 (40)</td>
<td>61 (47)</td>
</tr>
<tr>
<td>Employed, n (%)</td>
<td>126 (49)</td>
<td>64 (51)</td>
<td>62 (48)</td>
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<tr>
<td><strong>Lifestyle related factors</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>45 (18)</td>
<td>23 (18)</td>
<td>22 (17)</td>
</tr>
<tr>
<td>Mean alcohol consumption, units / wk</td>
<td>6 ± 7</td>
<td>5 ± 7</td>
<td>7 ± 8</td>
</tr>
<tr>
<td><strong>Clinical profile, diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes, n (%)</td>
<td>141 (55)</td>
<td>66 (53)</td>
<td>75 (58)</td>
</tr>
<tr>
<td>Insulin-treated Type 2, n (%)</td>
<td>69 (49)</td>
<td>35 (53)</td>
<td>34 (45)</td>
</tr>
<tr>
<td>Mean duration of diabetes in Type 1, y</td>
<td>21 ± 13</td>
<td>20 ± 12</td>
<td>22 ± 15</td>
</tr>
<tr>
<td>Mean duration of diabetes in Type 2, y</td>
<td>9 ± 8</td>
<td>8 ± 8</td>
<td>9 ± 9</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>28 ± 5</td>
<td>27 ± 5</td>
<td>28 ± 5</td>
</tr>
<tr>
<td>Mean A1c level, %</td>
<td>7.4 ± 1.3</td>
<td>7.4 ± 1.6</td>
<td>73 ± 1.6</td>
</tr>
<tr>
<td>Diabetes complications, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td>25 (10)</td>
<td>11 (9)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>11 (4)</td>
<td>5 (4)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>30 (12)</td>
<td>17 (14)</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Foot ulcers</td>
<td>21 (8)</td>
<td>9 (7)</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Mean depressive symptoms</td>
<td>28 ± 7</td>
<td>29 ± 7</td>
<td>28 ± 7</td>
</tr>
<tr>
<td>(CIS-D, range 16-60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosed with MDD (WHO CIDI), n (%)</td>
<td>146 (57)</td>
<td>71 (57)</td>
<td>75 (58)</td>
</tr>
<tr>
<td>Current AD use, n (%)</td>
<td>28 (11)</td>
<td>14 (11)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Mean diabetes-specific emotional distress</td>
<td>40 (19)</td>
<td>42 (19)</td>
<td>38 (19)</td>
</tr>
<tr>
<td>(PAID, range 0-100)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Data are expressed as mean ± SD, unless stated otherwise. MDD, major depressive disorder.

"Intervention and control group did not significantly differ (P > 0.05 in all cases) on any of the socio-demographic or clinical baseline characteristics.

**Per-protocol analyses**

Of those randomized to the intervention group, 53 (42%) completed the entire eight-lesson course, 30 (24%) completed no lesson at all, and 7 (6%) never logged into the course. Other participants dropped out equally divided over the course. The 53 completers and the 72 noncompleters of the course did not significantly differ on any of the measured baseline characteristics.
Stranger improvements in depressive symptoms and diabetes distress were found for completers of the course compared with the control group (both $P < 0.001$).

Effect sizes found at the 1-month follow-up were moderate to high for depressive symptoms ($d = 0.70, 95\% CI 0.59 – 0.82$). When calculated for the subgroup with elevated distress at baseline, we found a moderate effect size of $d = 0.58 (95\% CI 0.38 – 0.78)$ at the 1-month follow-up (intervention group $n = 30$, control group $n = 60$).

At postassessment and at the 1-month follow-up, a significantly higher percentage of the intervention group than the control group could be classified as “clinically significant improved” (1-month follow-up, 56\% vs. 24\%, $P < 0.001$).

Conclusions

This study is the first to demonstrate the effectiveness of a Web-based CBT depression intervention in adults with type 1 or type 2 diabetes. The intervention was shown to effectively reduce depressive symptoms and diabetes-related distress equally for type 1 and type 2 diabetes. In interpreting the findings of this study, we should acknowledge the strengths and limitations of the study.

The most important strength of this study was its strong design: a well-performed randomized controlled trial. We were able to attract and enroll a large number of adult patients with type 1 or type 2 diabetes who were apparently all actively looking for treatment, and of whom 57\% had a clinically significant depression. A major strength of the developed depression intervention was that it was based on the proven effective and well-known CBT Coping with Depression course developed by Lewinsohn. Another important strength of the intervention was that it was made diabetes-sensitive, by which it complied with the wishes and needs of diabetic patients.

Regarding the external validity (i.e. generalizability) of the study results, we should acknowledge that we included patients who were relatively homogenous demographically. This is likely related to the use of Internet, which may be less accessible to elderly, lower educated, and ethnic minorities. The use of the Internet, however, is rapidly expanding across society, including among these minorities.190

Furthermore, our method of recruiting participants via a freely accessible Web site could have led towards a selection bias by including patients who a priori believed in the effectiveness of a Web-based intervention and who were highly motivated and proactive. In future studies, we recommend questionnaires measuring patients’ a priori confidence in the effectiveness of the therapy, their motivation, and the reason for participating.

We thought it was unethical to have a follow-up period longer than 12 weeks because patients all suffered from elevated depressive symptoms or even a major depressive disorder and were therefore in need of treatment. Because the follow-up assessment was 1 month after treatment, we cannot draw between-group conclusions about long-term effects of the intervention. Within-group analyses are planned on data up until 6 months after treatment.

Study attrition was high, in line with other studies on Web-based therapy.95 191

192 Study attrition was 28\% in the control group compared with 42\% in the intervention group, which may be partly because the controls were awaiting treatment and therefore were more motivated. Although using state-of-the art methods for imputing missing data provided us with the best estimation of real data, also correcting for differences in study attrition in the intervention and control group, we should acknowledge that “true” data are preferable in any case. Future studies should seek to use effective strategies to minimize the problem of study attrition rates.

In contrast to our expectations, the participants diabetes was relatively well controlled, with a baseline mean $A_1$ of 7.4\%, despite comorbid depression and high levels of diabetes distress. The reason for this is unclear. One explanation could be that
the patients wishing to join the study were characterized by a strong motivation to stay on track with their diabetes. A subgroup analysis in those who were poorly controlled also did not show an effect of the intervention. However, this may be due to lack of power in this analysis, merely including 27% of the study population.

Although diabetic patients in the Netherlands usually visit their treating physician every 3 months, A1c was not measured every 3 months. In future studies we advise that additional A1c measurements are performed to assure accurate data for the purpose of the study.

Moreover, a follow-up of 1 month may have been too short to capture meaningful changes in A1c values. Decrease of depressive symptoms is assumed to indirectly affect glycemic control by stress hormone reduction or diabetes self-care activities. We plan to examine whether change in depression scores is associated with changes in self-care activities in the near future.

Dropout of the intervention is known to be common in both face-to-face and Web-based depression treatments, probably because depressed patients often lack energy, have low self-esteem, and low levels of optimism.193, 194 Given the substantial differences found between ITT and PP results in our study (with better results for PP), we may expect that with more patients completing their treatment, this would result in higher effect sizes. Future studies should explore strategies that can help to lower dropout rates in depression treatment and thus improve outcomes, in online as well as in face-to-face treatment.

In developing our online intervention, we incorporated issues related to coping with diabetes while preserving the integrity of CBT. It would be interesting and relevant to test the superiority of our intervention to a similar generic web-based depression intervention in diabetic patients in a randomized controlled trial.

Considering its delivery by the Internet, our intervention has the potential to have a large reach and social impact. The cost-effectiveness of web-based depression interventions has been demonstrated in the general population.195 Although the Internet is not yet readily available around the world, its use is growing fast, offering a unique opportunity to provide effective support for diabetes patients in need of depression treatment.
CHAPTER 6

Is a severe clinical profile an effect-modifier in web-based diabetes-specific depression treatment?

Secondary analyses from a randomized controlled trial.
Abstract

Background  Depression and diabetes are two highly prevalent and co-occurring health problems. Web-based, diabetes-specific cognitive behavioural therapeutic (CBT) depression treatment is effective in diabetes patients, and has the potential to be cost-effective and to have large reach. A question which remains is whether the effectiveness differs for patients with seriously impaired mental health compared with patients with less severe mental health problems.

Objective  To test whether the effectiveness of web-based diabetes-specific CBT for depression differs in patients with and without diagnosed major depressive disorder (MDD), diagnosed anxiety disorder, or elevated diabetes-specific emotional distress (DM-distress).

Methods  Data of 255 diabetes patients with elevated depression scores, who participated in an RCT, conducted in 2008-2009, were used to do secondary analyses, in order to study whether MDD, anxiety disorder, and elevated DM-distress are effect-modifiers in the treatment of depressive symptoms with web-based diabetes-specific CBT.

Results  MDD, anxiety disorder, and elevated DM-distress were no significant effect-modifiers in the treatment of depressive symptoms with web-based diabetes-specific CBT.

Conclusions  This web-based diabetes-specific CBT depression treatment is suitable for use in patients with severe mental health problems and those with a less severe clinical profile.
Introduction

With an estimated world prevalence of 285 million people, diabetes mellitus has reached epidemic levels globally. Affecting ten to twenty percent of the adult diabetes patients, depression is to be regarded a common co-morbid health problem. Depression in diabetes negatively impacts quality of life, diabetes outcomes and increases mortality rates. It is therefore of great importance that depression in diabetes is treated.

A recent meta-analysis has shown that depression in diabetes patients can be effectively treated with various anti-depressant treatments, showing the highest effect sizes for psychological treatment (Cohen’s $d = 0.58$, with 95% CI $0.27$ to $0.77$), compared with pharmacologic treatment (Cohen’s $d = 0.47$, with 95% CI $0.66$ to $0.27$) or collaborative care (Cohen’s $d = 0.29$, with 95% CI $0.74$ to $0.16$).

Nevertheless, in a substantial part of diabetes patients, compact depression remains untreated. Under-representation of complaints, under recognition of depressive symptoms by health care providers and inadequate referral can account for this. Another reason for untreated depression in diabetes patients is the negative stigma of mental health care among patients who are treated in somatic health care, or they do not feel at home in a mental health care setting. A depression treatment that specifically addresses elevated diabetes-specific emotional distress (DM-distress) could help overcome this last barrier to treatment, and has been advised to be developed. The VU university medical centre has recently developed such a CBT depression intervention, specifically tailored to the needs of diabetes patients by incorporation of diabetes-specific topics, for example coping strategies on diabetes-specific issues.

Providing psychological interventions via the Internet could help overcome barriers to treatment related to travelling distance and time, e.g. it has the potential to avoid reluctance to therapy in patients who are ashamed of being in need for psychological help, and it allows patients to work at home, in their own pace and familiar environment, while saving them time, burden, and costs from travelling. Therefore, an internet-administered intervention has the potential to have a broad reach, it can also save therapists time, and thus reduce waiting-lists. Providing psychological interventions via the Internet can be a major advantage specifically for diabetes patients, since they already spend much time in (somatic) health care and severe diabetes complications can cause physical impairments, causing difficulties with mobility. Therefore, the new diabetes-specific depression intervention was offered via the Internet.

The web-based diabetes-specific depression intervention (DC.nl; Diabetergestemd.nl) was based upon the effective web-based CBT depression intervention Color Your Life, which was based on Lewinsohn’s effective and well-known Coping with Depression course. The effectiveness of DCnl was shown in a randomized controlled trial. A commonly heard criticism in studies regarding web-based CBT depression treatment is that most studies do not differentiate between elevated symptoms of depression (subclinical depression) and diagnosed depression in the strict sense (MDD, major depressive disorder). This causes clinicians being in need for more convincing evidence that online CBT can help their patients with subclinical depression but also those with MDD, especially since the current guidelines for depression treatment indicate that patients with subclinical depression warrant a different treatment (low-intensity psychosocial interventions, such as guided self-help) than do patients with MDD (high intensity psycho-social intervention, such as individual CBT). In our study, we administered a diagnostic instrument, which enabled us to make a clear distinction between patients with subclinical depression and patients with MDD.

Examination of potential differences in effectiveness in both subgroups provides
substantial information regarding the applicability of the intervention in clinical practice.

The elevated prevalence of anxiety disorders in type 1 and type 2 diabetes in comparison with prevalence rates in general population has been demonstrated in a systematic review. Treatment literature indicates that the combination of MDD and anxiety is more difficult to treat than MDD only. Therefore, we examined effect-modification of anxiety disorder in our study sample. Furthermore, since studies on the prevalence of co-occurring anxiety and affective disorders in diabetes patients have yielded mixed results, we were interested in exploring the co-occurrence of anxiety disorders in patients with MDD.

A common criticism in the field of studies concerning psychological interventions in diabetes patients, is a lack of accurate differentiation between MDD, anxiety disorder, subclinical depression and elevated diabetes-specific emotional distress (DM-distress). Previous reports emphasized that diabetes patients with elevated symptoms of depression are not all necessarily clinically depressed, but rather, are suffering from high levels of diabetes-related distress. It has also been suggested that since DM-distress and MDD are not the same phenomenon, we need to tailor interventions to the specific needs of these subgroups. Since DGNL is specifically tailored to patients suffering from elevated DD, these patients may particularly benefit from the intervention. Since these two concepts are highly related, reduction of diabetes-distress may result in reduction of depressive symptoms. Therefore, we tested whether the online diabetes-specific depression intervention was more effective in patients with baseline elevated DD.

To summarize, in this article we aim to answer the following question: does the effectiveness of a web-based diabetes-specific CBT depression intervention differ for patients with or without MDD, in patients with or without an anxiety disorder, and in patients with or without elevated DD.

To the best of our knowledge, this is the first study that uses data of a randomized controlled trial to perform analyses to test effect-modification of several subgroups of diabetes patients in the effectiveness of a web-based diabetes-specific CBT depression treatment.

**Methods**

**Participants and procedure**

We conducted a randomized controlled trial (RCT) in 2008-2009, in which $n = 255$ adult diabetes patients with elevated depressive symptoms (having a score of 16 or higher on the Centre for Epidemiological Studies Depression scale), were randomly assigned to the web-based diabetes-specific depression intervention ($n = 125$) or a 12-week wait-list control group ($n = 130$). Data of this RCT were used to do our secondary analyses on. The design of this RCT on the effectiveness of the web-based diabetes-specific depression intervention have been described elsewhere. The Medical Ethics Committee of the VU University Medical Centre approved the study. The results of the RCT have also been described elsewhere. In short, the intervention was effective in reducing depressive symptoms and diabetes-specific emotional distress.

**Intervention**

Participants assigned to the intervention group, individually went through an online course, based on the principles of Cognitive Behavioural Therapy (CBT). Theoretically, this course is based on the social learning theory according to which depression is associated with a decrease in pleasant and an increase in unpleasant person-environment interactions. People's problems are viewed as behavioural and cognitive patterns which can be unlearned or relearned. The intervention has been described in
more detail elsewhere. In short, the course consists of eight consecutive weekly lessons, consisting of psycho-education and focused on skills such as relaxation, cognitive restructuring (including worrying), social skills, and how to increase the number of pleasant events, with written and spoken information and homework assignments with one-time feedback per lesson from a psychologist.

Sample characteristics
Baseline characteristics of our study sample were self-reported as part of the online assessment. Previous analyses confirmed successful randomization: intervention and control group did not statistically significant differ regarding demographic or clinical characteristics at baseline (all $P$-values $\geq 0.05$).

Outcome measure
Depressive symptoms were assessed with the Dutch version of the Centre for Epidemiological Studies Depression scale (CES-D). The CES-D is a validated self-report screening instrument which measures the frequency with which participants have experienced specific depressive symptoms within the preceding week. The questionnaire contains 20-items with a 4 point Likert-scale. The total score can range from 0 to 60, where higher scores indicate more depressive symptoms. In Dutch samples, a cut-off point of 16 or higher is generally accepted as indicative of clinical depression.

Potential effect-modifiers
Based on our research questions, we selected the following three potential effect-modifiers: major depressive disorder (MDD) (yes or no), an anxiety disorder (yes or no), and high versus low level of elevated diabetes-specific emotional distress (DM-distress).

In order to test effect modification, the course of depressive symptoms at baseline, post-treatment and one-month follow up between intervention and control group were compared for each potential effect-modifier.
Statistical analyses
To test effect-modification, Generalized Estimated Equations (GEE) analyses were performed using three-way interaction terms (group x time x potential effect-modifier) to examine whether being diagnosed with major depressive disorder (MDD) (yes / no), anxiety disorder (yes / no), and having elevated diabetes-specific emotional distress (DM-distress) (PAID ≥ 40 / < 40) were significant effect-modifiers in the treatment effect. All analyses were corrected for baseline depression scores to gain insight into the relative degree of change, and for time between baseline measurement and post-measurement. Also, all potential effect modifiers were examined on baseline differences for all of the measured socio-demographic and clinical variables, and all analyses were corrected for these differences.

Since attrition was not completely at random, we imputed missing data using the Multiple Imputation technique, with Stata 10.0 software. Multiple Imputation minimally alters variance of data and thus gives best estimates of missing data. All further statistical analyses were performed using complete data, with either Stata 10.0 or SPSS 15.0 software. All results were based on intention to treat analyses.

Results
Baseline characteristics
Baseline socio-demographic and clinical characteristics of our study sample are presented in Table 1, and have been described in detail elsewhere.195

Potential effect-modifiers
As shown in Table 1, over half of the patients in our study sample (n = 146, 57%) were diagnosed with a major depressive disorder (MDD), of which the majority (131 / 146, 90%) suffered from a single episode of MDD, not from a recurrent depression. About half of the patients diagnosed with MDD (n = 146) comorbidly suffered from an anxiety disorder (n = 69 / n = 146, 47%) and about half suffered from comorbid elevated diabetes distress (n = 80 / n =146, 55%) (Table 2).

Examining baseline differences, showed that of those patients who had been diagnosed with MDD (n = 146), a higher percentage had type 2 diabetes patients (64% vs. 43%, P = 0.001) and a lower percentage used anti-depressive medication (7% compared with 15%, P < 0.001) compared with those without MDD (n = 109). Furthermore, MDD patients reported higher baseline symptoms of depression (mean CES-D 30 ± 7 vs. 26 ± 7, P < 0.001) and higher levels of diabetes-specific emotional distress (DM-distress) (mean PAID 42 ± 20 vs. 37 ± 17, P = 0.02). About half (n = 69, 47%) suffered from a co-morbid anxiety disorder.

About a third of the total study sample (n = 95, 37%) was diagnosed with an anxiety disorder. Patients diagnosed with anxiety disorder had higher baseline depressive symptoms (mean CES-D 31 ± 8 vs. 27 ± 7, P < 0.001) and DM-distress (mean PAID 48 ± 18 vs. 36 ± 18, P < 0.001) and did not significantly differ on any socio-demographic variable.

Half of our study sample (n = 127, 50%) suffered from elevated DD. The patients with elevated DM-distress were younger (mean age 47 ± 13 (53 ± 12, P = 0.001), were more often women (67% vs. 55%, P = 0.045), had higher baseline depression scores (mean CES-D 31 ± 7 vs. 26 ± 6, P < 0.001), and were more often diagnosed with anxiety disorder (50% vs. 25%, P < 0.001) than those without elevated diabetes distress.
Table 1. Baseline socio-demographic and clinical characteristics of study sample at baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n = 255)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Socio-demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Mean age, y</td>
<td>50 (12)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>155 (61)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>244 (96)</td>
</tr>
<tr>
<td>Marital state – with partner, n (%)</td>
<td>199 (78)</td>
</tr>
<tr>
<td>Education level, n (%)</td>
<td></td>
</tr>
<tr>
<td>No formal qualifications</td>
<td>8 (4)</td>
</tr>
<tr>
<td>High school or lower / middle vocational qualifications</td>
<td>136 (53)</td>
</tr>
<tr>
<td>College qualifications or more</td>
<td>111 (44)</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms (CES-D, range 16-60)</td>
<td>28 (7)</td>
</tr>
<tr>
<td>Mean diabetes-specific emotional distress (PAID, range 0-100)</td>
<td>40 (19)</td>
</tr>
<tr>
<td>Type 2 diabetes, n (%)</td>
<td>141 (55)</td>
</tr>
<tr>
<td>Mean HbA1c level, %</td>
<td>7.4 (1.3)</td>
</tr>
<tr>
<td>Self-reported diabetes complications, n (%)</td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td>25 (10)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>30 (12)</td>
</tr>
<tr>
<td>Foot ulcer</td>
<td>21 (8)</td>
</tr>
<tr>
<td><strong>Diagnosis: Depressive Disorder (WHO-CIDI)</strong></td>
<td></td>
</tr>
<tr>
<td>MDD, n (%)</td>
<td>146 (57)</td>
</tr>
<tr>
<td>MDD, single episode, mild</td>
<td>62 (24)</td>
</tr>
<tr>
<td>MDD, single episode, moderate</td>
<td>48 (19)</td>
</tr>
<tr>
<td>MDD, single episode, severe</td>
<td>21 (8)</td>
</tr>
<tr>
<td>MDD, recurrent episode, mild</td>
<td>8 (3)</td>
</tr>
<tr>
<td>MDD, recurrent episode, moderate</td>
<td>4 (2)</td>
</tr>
<tr>
<td>MDD, recurrent episode, severe</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Dysthymic Disorder</td>
<td>28 (11)</td>
</tr>
<tr>
<td><strong>Diagnosis: Anxiety disorder, n (%)</strong></td>
<td>95 (37)</td>
</tr>
<tr>
<td>Generalized Anxiety disorder</td>
<td>59 (23)</td>
</tr>
<tr>
<td>Social Phobia</td>
<td>24 (9)</td>
</tr>
<tr>
<td>Panic Disorder</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Panic Disorder with Agoraphobia</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Specific Phobia</td>
<td>52 (21)</td>
</tr>
<tr>
<td>Blood-Injection-Injury Type</td>
<td>22 (9)</td>
</tr>
<tr>
<td>Environment Type</td>
<td>15 (6)</td>
</tr>
<tr>
<td>Situational Type</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Animal Type</td>
<td>6 (3)</td>
</tr>
</tbody>
</table>

Data are given as mean (SD) unless otherwise indicated.  
Abbreviations: CES-D, Centre for Epidemiologic Studies-Depression scale; PAID, Problem Areas In Diabetes scale; MDD, Major Depressive Disorder; WHO-CIDI, World Health Organization Composite International Diagnostic Interview; AD; HbA1c, glycosylated hemoglobin.
Table 2. The amount of the study population that suffers from a diagnosed depression, a diagnosed anxiety disorder and elevated diabetes-specific emotional distress (PAID >40).

<table>
<thead>
<tr>
<th>Study population</th>
<th>Diabetes-specific emotional distress</th>
<th>No diabetes-specific emotional distress</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD</td>
<td>Anxiety 69 (27)</td>
<td>46 (18)</td>
</tr>
<tr>
<td></td>
<td>146 (57)</td>
<td>23 (9)</td>
</tr>
<tr>
<td></td>
<td>No Anxiety 77 (30)</td>
<td>34 (13)</td>
</tr>
<tr>
<td></td>
<td>109 (43)</td>
<td>43 (17)</td>
</tr>
<tr>
<td></td>
<td>No MDD Anxiety 26 (10)</td>
<td>17 (7)</td>
</tr>
<tr>
<td></td>
<td>83 (33)</td>
<td>9 (4)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>127 (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>128 (50)</td>
</tr>
</tbody>
</table>

Data are presented as number (percentage of total study sample of n = 255).

Table 3. Comparing the effectiveness of a web-based diabetes-specific depression therapy on symptoms of depression (CES-D), testing effect modification by depression status (MDD versus no MDD), anxiety disorder (yes/no), or high level of diabetes-specific emotional distress (yes/no).

<table>
<thead>
<tr>
<th>CES-D score</th>
<th>Intention to treat Analyses n = 125 / 130</th>
<th>Pre treatment</th>
<th>Post treatment</th>
<th>One-month follow-up</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CBT WL</td>
<td>CBT WL</td>
<td>CBT WL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDD</td>
<td>30 (7) 30 (7)</td>
<td>21 (11)</td>
<td>24 (9)</td>
<td>20 (12)</td>
<td>.489</td>
</tr>
<tr>
<td>No MDD</td>
<td>27 (7) 26 (7)</td>
<td>18 (9)</td>
<td>21 (8)</td>
<td>19 (10)</td>
<td></td>
</tr>
<tr>
<td>Anxiety disorder (CIDI)</td>
<td>32 (7) 31 (8)</td>
<td>23 (11)</td>
<td>25 (9)</td>
<td>22 (11)</td>
<td>.706</td>
</tr>
<tr>
<td>No anxiety disorder</td>
<td>27 (7) 26 (6)</td>
<td>19 (10)</td>
<td>21 (8)</td>
<td>19 (11)</td>
<td>.706</td>
</tr>
<tr>
<td>Elevated diabetes-specific emotional distress (PAID ≥ 40)</td>
<td>31 (7) 31 (8)</td>
<td>22 (11)</td>
<td>24 (9)</td>
<td>21 (12)</td>
<td>.924</td>
</tr>
<tr>
<td>No elevated diabetes-specific emotional distress (PAID &gt;40)</td>
<td>26 (7) 26 (6)</td>
<td>18 (10)</td>
<td>22 (9)</td>
<td>18 (10)</td>
<td>.924</td>
</tr>
</tbody>
</table>

Data are given as mean (SD).

CBT indicates cognitive behavioral therapy condition; WL, waiting – list control condition; CES-D, Centre for Epidemiologic Studies-Depression scale; MDD, Major Depressive Disorder.

Both MDD and Anxiety disorder are diagnosed using the WHO CIDI, World Health Organization Composite International Diagnostic Interview.

Our statistical tests relied on generalized estimating equation (GEE) analyses. P-values indicate level of significance of effect-modification. All analyses are adjusted for baseline CES-D scores, baseline between-group differences on socio-demographic variables, and differences in time between pretreatment and post treatment. Table represents uncorrected data.
**Potential effect-modifiers in of the treatment effect**

GEE analysis showed that "being diagnosed with major depressive disorder (MDD)" ($P = 0.49$) was not a significant effect-modifier in the treatment effect on depressive symptoms (Table 3). In other words, corrected for baseline differences in depressive symptoms and diabetes-distress, type of diabetes, use of anti-depressant medication, and the time between pre- and post-treatment, we did not find significant differences in reduction of depressive symptoms for the intervention group versus control group, for patients with MDD compared with patients without MDD.

GEE analysis also revealed that being diagnosed with an anxiety disorder also was not a significant effect-modifier ($P = 0.71$) (Table 3). In other words, corrected for baseline differences in depressive symptoms and diabetes distress, and the time between pre- and post-treatment, we did not find significant differences in reduction of depressive symptoms for the intervention group compared with control group, did not significantly differ for patients with or without MDD, anxiety disorder and with or without elevated DD.

Finally, having elevated DM-distress ($P = 0.92$), was no significant effect-modifier in the treatment effect on depressive symptoms (Table 3). This analysis was corrected for age, gender, baseline depression scores, and diagnosis anxiety disorder.

**Discussion**

The main aim of this study was to test whether an MDD-diagnosis, a diagnosis anxiety disorder or having elevated diabetes-specific emotional distress (DM-distress) were significant effect-modifiers for web-based diabetes-specific cognitive behavioural therapy (CBT) depression treatment. Results of our study clearly show that this was not the case.

In interpreting the results of our study, we should acknowledge several strengths and limitations of the study. The most important strengths are the randomized controlled trial design and the innovative character of the study. This is the first study that tests the effectiveness of web-based diabetes-specific depression treatment in different subgroups of patients. Moreover, we administered a diagnostic interview and used validated instruments for measuring depressive symptoms and diabetes-distress. Furthermore, by administering both a screener for generic emotional distress (CES-D) as well as a disease-specific emotional distress questionnaire (PAID), we were able to differentiate between diabetes-specific emotional distress (DM-distress) and generic emotional distress, a distinction that is often not recognized.

Examining effect-modification was not the primary aim of our RCT. Therefore, this study was not powered at detecting significant differences in effect between patients with and without MDD, anxiety and elevated DD. Since our study sample is probably too small to draw definite conclusions, we can only report on the results found in our study. A study which is specifically powered at finding these differences is advised, in order to confirm and generalize the results outside or our study sample.

Regarding external validity of our results, we should take into account that our sample consisted largely of highly educated, Caucasian, without poor glycaemic control and we did not include older patients: merely 9%, $N = 23$ was aged 65+. Considering higher prevalence of diabetes in people with lower social economic status, non-Dutch background, diabetes patients who suffer from complications, thus in poor glycaemic control, and considering the ageing of the population in general and the related increase of older patients with type 2 diabetes, an explorative study specifically including these subgroups of patients (elderly, ethnic minorities, patients in poor glycaemic control) is advised in order to confirm effectiveness in these subgroups.

Regarding MDD, we would like to emphasize that the most severe cases of depression were excluded from our study: patients who had current suicidal ideation, a
history of suicide attempts, and a history of admission in a psychiatric hospital or had comorbid psychotic features. We also observed that the majority of the patients with MDD diagnosis suffered from a single episode of MDD, not from a recurrent depression. This, while MDD has shown more recurrent in diabetes patients. Perhaps the underrepresentation of patients with recurrent depressive episodes in our study can be explained by these patients already having tried several forms of depression treatment and therefore less willing to try a new form of therapy (web-based therapy).

Periodic assessment and subsequent adequate referral to depression treatment has been advised to be incorporated in diabetes care. \(^{201}\) Regarding referral to web-based treatment of depression in diabetes, screening for depression would seem advisable, without the need to diagnose MDD, since based on the results of this study, we would advise to consider the web-based therapy suitable for both diabetes patients suffering from MDD and patients who merely suffer from subclinical depression.

Internet interventions are advised to be incorporated in the stepped care approach of depression treatment. \(^{202, 203}\) However, the position of internet interventions in a stepped care model is yet unclear. Based on the results of this study, we would advise to consider the web-based therapy suitable for both diabetes patients suffering from MDD and patients who merely suffer from subclinical depression.

We found no significant differences in the effectiveness of web-based depression treatment between patients with or without an anxiety disorder in our study. This would suggest that having anxiety disorder is no contraindication for this treatment. Diagnosing anxiety can be informative, but does not seem strictly necessary.

Unfortunately, since our study was not powered on including patients with MDD and anxiety disorder, we were unable to test whether specifically MDD was more difficult to treat when having comorbid anxiety, but in stead examined effect-modification in the full sample of sub clinically depressed and MDD patients. Since in our study sample a substantial group suffered from both MDD and anxiety disorder, this stresses the importance of testing effect-modification of anxiety disorder in a sample of diabetes patients with MDD.

Furthermore, in contrary to our expectation, we did not find significant differences between the effects of DGNL in patients suffering from elevated DM-distress and in those without distress. Although not finding significant differences in effectiveness, it might be that diabetes patients with diabetes distress feel more at home in a disease-specific depression intervention. In a future study, comparing the diabetes-specific intervention with a generic web-based depression intervention on effectiveness and attractiveness from a patient perspective would be of great importance.

Besides the precautions in external validity of our results, the information found in this paper is important considering implementation of the intervention in clinical practice. With exception of the most severe cases (elevated risk of suicide, psychotic features), the effectiveness of the web-based intervention did not show to significantly differ for patients with and without a diagnosis MDD. In positioning our intervention in the stepped-care model for depression treatment, this web-based intervention can be considered a proper treatment for all patients and can be administered as a second step in stepped-care, after the less invasive steps, such as watchful waiting and psycho-education. \(^{203}\)

Conclusions

Learning whether a web-based diabetes-specific depression treatment intervention is more or less effective for patients suffering from a severe and complicated clinical profile, could help us formulate recommendations regarding improvement of the intervention, and for referral to and implementation of the intervention in clinical
practice, and is therefore of great clinical and social relevance.

No significant differences were found in the effectiveness of a web-based, diabetes-specific depression intervention in diabetes patients suffering from a severe clinical profile, and for patients suffering from less severe emotional problems.

The web-based diabetes specific depression treatment seems suitable for a broad range of diabetes patients. Implementation of the intervention in regular diabetes health care is advised. Given its web-based administration, DG.nl has the potential to be cost-effective and to have large reach.¹⁷⁴
**Importance of this thesis**

Both diabetes and depression are major global health problems, resulting in impaired quality and quantity of life, and affecting millions of people worldwide (see Figure 1), while both are rapidly increasing. Diabetes and depression are likely to co-occur, resulting in impaired quality of life and poor health outcomes. Prevalence rates vary between countries and for type 1 and type 2 diabetes, but based on estimations, worldwide approximately 136 million adults will suffer from both diabetes and clinically relevant depression in 2030.

![Figure 1](image.png)

**Figure 1.** Estimated point prevalence of global prevalence of diabetes in 2025 in percentages (left) and the estimated daily adjusted life years (DALYs, the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability) of unipolar depression in 2004 per 100,000 inhabitants (right) (source: International Diabetes Federation and World Health Organisation via Wikipedia.nl)

Depression is a common comorbid health problem in diabetes patients that often remains untreated. Moreover, diabetes-specific emotional distress appears to be particularly common in depressed diabetes patients. The burden of having diabetes, having a chronic disease to care for day-in-day out, and having (the prospect of future) complications of diabetes are important factors that can contribute to depression.

Therefore, diabetes-specific treatment of depression has been advised in diabetes patients, in order to enlarge effects of depression treatment in diabetes, to overcome the negative stigma of mental health care in diabetes patients by acknowledging that depression is common in diabetes, and to enlarge effects of treatment on diabetes outcomes.

The emerging Internet (see Figure 2) provides the opportunity to deliver interventions without limitations due to distance or time, thus expanding reach, and is especially fit for reaching the main diabetes population: adults of working age in developing countries.

A diabetes-specific depression intervention provided through the Internet has the potential to substantially add to attacking the global problem of depression in diabetes patients.
Conclusions of this thesis

Main aim of this thesis was to study the effectiveness of a web-based diabetes-specific depression intervention for adults with type 1 and type 2 diabetes in a randomised controlled trial (RCT). The detailed study protocol of this RCT is presented in chapter 2. We successfully developed the intervention, which has been described in chapter 4. In the key chapter of this thesis, chapter 5, the RCT is described, of which the main conclusion is:

"A web-based CBT depression intervention is effective in reducing depressive symptoms in type 1 and type 2 adult diabetes patients who were suffering from subclinical depression or major depressive disorder, with a moderately high significant effect size (d = 0.29 in intention-to-treat analysis and d = 0.70 in per protocol analysis)."

Additionally, the intervention appeared to be effective in reducing diabetes-specific emotional distress. However, we did not find an effect of the web-based intervention on glycaemic control. This may be due to the fact that the study sample was relatively well-controlled at baseline (floor effect). Furthermore, we conclude that the effectiveness of the intervention in reducing depressive symptoms was not modified by: being diagnosed with major depressive disorder (MDD), anxiety disorder or elevated diabetes-specific emotional distress (chapter 6).

In data from another study, a large depression in diabetes screening study in the Netherlands, we examined how depressive symptoms and diabetes-specific emotional distress are related to glycaemic control (chapter 3). We conclude that the relation between depression and glycaemic control is mediated by diabetes-specific emotional distress. Currently, this finding was also confirmed in another study. This finding implies that when treating depression in diabetes, benefits on glycaemic control can be expected in patients where reduction of diabetes-specific emotional distress occurred. These results confirm the importance of addressing diabetes-specific emotional distress in depression treatment.
The results of the studies which are presented in this thesis and the literature described in this thesis, lead toward a model which explains the potential mechanism behind a beneficial impact of diabetes-specific depression treatment with CBT in the case of diabetes, which is presented in **Figure 3**. This model explains that web-based diabetes-specific CBT treatment (via the CBT skills: cognitive restructuring, behavioural reinforcement, social skills, relaxation) leads towards improved mood and behaviour (presented in the left box), mutually impacting each other. Behavioural improvements and the reduction in diabetes-specific emotional distress lead towards improved glycaemic control and overall improved physical health (presented in the middle box). These somatic improvements lead towards a prevention of the onset of diabetes complications, while the skills learned in the CBT leads toward a prevention of depression recurrence (presented in the upper right box). Finally the model shows that CBT, via emotional improvements, improved physical health and prevention of depression, complication and comorbidity adds to an improved current and future quality of life (presented in the bottom right box).

![Figure 3. Model explaining the mechanism behind the beneficial impact of CBT on mental and physical health in the case of depression and diabetes](image)

**Methodological considerations**

In interpreting the findings of this study, we should acknowledge several strengths and limitations of the study. In the following sections the methodological considerations of the randomised controlled trial will be discussed.

**Adjustments to the protocol**

Before the start of the study, we first described the way we planned to conduct our randomised controlled trial (**chapter 2**). Two adjustments were made to this protocol.

A clear distinction should be kept in mind between elevated symptoms of depression (subclinical depression) and a diagnosed depressive disorder (MDD, major depressive disorder). At the start of the study, we planned to include patients with MDD only. However, during recruitment, we noticed that a substantial part of the patients who signed up for the study suffered from subclinical depression, and not MDD. Due to inclusion reasons we therefore chose to make our inclusion criteria less strict and to include patients with sub threshold depression.
Since subclinical depression is also known to be associated with impaired quality of life of patients, and an important predictor for developing MDD in diabetes, treatment of subclinical depression is of great importance. Web-based therapy proved to be effective in treating subclinical depression, which made our decision justifiable.

Administering a diagnostic interview and including both patients with sub threshold depression and with MDD in our study, provided us with the opportunity to compare these groups of patients regarding the effectiveness of our intervention.

Furthermore, at the start of this study, we excluded patients using antidepressive medication (AD). Since this showed to jeopardize our inclusion, we decided to include patients using AD after all. In our analyses we corrected for AD use.

**External validity**
To ensure external validity, allowing for generalisation of results of our study to the whole population of adult diabetes patients with elevated symptoms of depression, the selection of patients for the study should aim at including a representative sample.

**Self-enrolment**
Web-based treatment is positioned as a first step or an add-on to traditional face-to-face or group treatment in the guidelines for depression treatment. Therefore, examining the intervention in a freely accessible environment provides the best representation of effect sizes in routine practice. This makes our RCT more a pragmatic trial rather than a trial conducted in a merely research environment.

Since our intervention was freely accessible and patients could register for the study themselves, without referral from a (mental) health care provider, this lowered the risk of referral bias, as described in chapter 4. However, selection bias could have occurred, attracting primarily highly motivated patients or patients with high confidence in the effectiveness of the intervention. Asking for patients’ motivation and confidence in the therapy therefore would have been advisable.

**Characteristics of study sample**
Primarily Caucasian, relatively well educated, with well controlled diabetes, Dutch speaking, computer literate and few elderly patients were enrolled in our study. Extrapolation of the results to patients with a lower level of education, ethnic minorities, elderly, and patients having a severe diabetes profile, for example indicated by having severe diabetes complications, therefore requires additional research.

Regarding severity in terms of psychological profile, about half of the patients included in our study were diagnosed with MDD. The majority of patients diagnosed with MDD suffered from a single episode of depression. It might be that patients who suffered from several episodes of MDD also received more treatment in the past and were therefore more sceptical regarding effectiveness of this new intervention.

Implementation of the web-based intervention in a stepped care model, could help to formulate recommendations regarding administering the intervention to patients with a single episode of MDD or those with recurrent episodes.

**Diagnostic validity**
*Web-based administration of questionnaires*
All of the questionnaires used in our study are validated and widely used. There are some studies showing that in internet-administered questionnaires higher cut-off scores should be used, probably due to greater anonymity when rating emotional issues on the internet at home, which might increase honesty and self-disclosure. Therefore, for questionnaires that haven’t been revalidated for administration via the Internet, establishing optimal cut-off scores is required.
Validity of questionnaires in diabetes patients

Both generic depression screening questionnaires and diabetes-specific emotional distress measures, have shown satisfactory sensitivity in case of screening for clinical depression (e.g. 87% sensitivity in CES-D (e.g. 81% sensitivity in PAID)). Therefore, for questionnaires that haven’t been revalidated for administration in diabetes patients, establishing optimal cut-off scores is required.

Study design

The effectiveness of the web-based diabetes-specific depression intervention was studied in a randomised controlled trial (RCT), which is the classical design of an experimental study. In an RCT, the experimental group, which is exposed to the intervention under investigation, is compared with a control group, which is not exposed. Random allocation to the experimental and control group guarantees the equivalence of both groups. Choosing the control condition, several options were thinkable, all having its advantages and disadvantages. A waiting list controlled trial provides optimal contrasts for the experimental group and does not keep people away from the desired services.

Internal validity

Internal validity of a study refers to whether causal relations are properly demonstrated and cannot be attributed to other factors.

Confounding

A major threat to the validity of causal inferences is confounding. In case of confounding, changes in the dependent variable are rather to be attributed to variations in a third variable, which is related to the manipulated variable. In our study, we corrected our analyses for use of additional depression treatment such as medication and psychotherapy.

Successful randomisation

Through randomisation, it is aimed to omit systematic differences between the comparison groups that exist before the start of the intervention, which can be a major threat to internal validity. Even in a randomised trial, checking for baseline differences between the compared groups is necessary. In our study sample, we did not find baseline differences between the two groups on any of the measured socio-demographic or clinical variables, confirming successful randomisation.

Attrition

In our study and in line with other studies on web-based therapy, we faced a high attrition rate (35%). Although using the state-of-the art method for imputing missing data provided us with the best estimation of real data, we should acknowledge that having “true” data of all participants is of course preferable in any case. In future, studies exploring strategies to reduce attrition rates, e.g. financial reward for study participation, is of great interest.

Sample size

To ensure statistical power, it is essential to include a sufficient number of participants in a study. The sample size in our RCT was calculated based on the expected difference
in the primary outcome variable (i.e. depressive symptoms). Based on a statistical power of 0.80, with an alpha of 0.05, 100 subjects were required in each group to be able to detect differences with an effect size of 0.35. With an expected 30% study drop-out, we determined the study sample size at 286 participants to be randomized. The final sample size was somewhat smaller ($n = 255$) than the calculated aimed sample size ($n = 286$). However, since we imputed missing data, we did perform analyses on the intended sample size (which was $n = 200$).

**Clinical relevance**
Besides finding statistically significant results, it is important to translate these results to clinical practice. Therefore, clinically significant change was determined, defined as having recovered and showing significant improvement on the CES-D. Recovery was defined as having a score below 16 on the CES-D. Improvement was determined following the suggestions of Jacobson and Truax, calculating a reliable change index (RC) [see chapter 5], which in our study came down to 5 points lowering on the CES-D. Patients who both improved and recovered were considered as being "clinically significant improved". A significantly higher percentage of the intervention group (41%) showed clinically significant improvement at one-month follow-up than the control group (24%, $P < 0.001$, based on intention to treat analyses).

**Ethical considerations**
Some ethical issues regarding our study deserve mentioning.

First, patients having current suicidal ideation or with a history of suicide attempt, were excluded from our study and advised to contact their general practitioner (GP) for advise on appropriate treatment. Perhaps a more proactive approach in terms of personally contacting the patients who indicate to have current suicidal ideation, after asking their consent to contact them, would seem advisable. Several patients with a history of suicide attempt(s) expressed their disappointment in being excluded from our study. Since, in literature, we do not find evidence that suicide attempt(s) in the past is a contraindication for web-based treatment and in order to avoid disappointment, it would be advisable to also include depressed patients with a history of suicide attempts in future depression studies. However, this may complicate obtaining Medical Ethical approval for the study.

Furthermore, when patients at post-measurement still suffered from elevated depressive symptoms, they were advised to contact their GP to discuss further treatment. Here, a more proactive approach may also be needed, e.g. informing the GP with the results of the assessment and treatment.

Privacy of digital patient information is an important issue in web-based treatment and should be guaranteed with help from experts in this field.

**Clinical implications**

**Effect size**
The effect size of our intervention appeared to be small in the intention-to-treat analyses ($d = -0.29$, 95% CI: -0.31 ~ -0.28) and moderate to high in per protocol analyses ($d = -0.70$, 95% CI: -0.71 ~ -0.69). In a recent meta-analysis on depression treatment in diabetes patients, the combined effect size of five studies on psychotherapy was large ($d = -0.58$, 95% CI: -0.71 ~ -0.36). These five studies included three per protocol analyses and two intention-to-treat analyses. Comparing our intention-to-treat effect sizes, ours are smaller than the other two (-1.11, CBT plus education, -0.92 individual supportive psychotherapy). General overestimation of effect sizes in studies regarding psychotherapy for depression treatment, due to low quality of many of these studies, may account for this.²³⁸ Comparing our data with the per
Drop-out
Drop-out is a common problem in depression treatment, probably inherent to the problem, since many depressed patients lack energy and hope and have low levels of self-esteem. These factors are strong predictors of drop-out.

Web-based interventions are known for its high drop-out rates. This might be explained by the fact that patients feel more embarrassed when having to cancel a face-to-face contact. In case of web-based therapy, patients are more anonymous and do not have to justify themselves for quitting therapy. Given the substantial differences found between ITT and PP results in our study, we would expect that when more efforts are made to encourage patients to complete the intervention, this could result in higher effect sizes. Future studies should explore strategies that can help to lower drop-out rates in depression treatment and thus improve outcomes of depression treatment, both in online as in face-to-face treatment.

Once patients have shown the motivation to accept treatment, we should make maximal efforts to try to keep them in treatment, thus reducing their current depressed affect and prevent future depression. If the web-based intervention does not show sufficient or fit for patients, we should discuss options for alternative treatment.

Diabetes outcomes
In chapter 5, we show that, next to reducing depressive symptoms, the intervention was effective in significantly reducing diabetes-specific emotional distress.

The RCT did not show beneficial effects of the intervention on glycaemic control. The relatively short follow-up period, and the fact that we have included a group with good glycaemic control (floor effect) could explain this. In future studies, including patients with poor glycaemic control, performing HbA1c measurements specifically for the study, and having a longer follow-up period of comparison between intervention and control group, can shed more light on the real effects of the intervention on glycaemic control.

Furthermore, chapter 3 of this thesis showed that glycaemic control was more strongly related to the level of diabetes-specific emotional distress than generic emotional distress. Therefore, comparing the effectiveness in diabetes patients with poor glycaemic control and who showed a reduction in diabetes-specific emotional distress with those not showing a reduction in distress, can confirm that beneficial effects of the intervention on glycaemic control are related to changes in diabetes-specific emotional distress.

Type of diabetes
Although acknowledging the substantial differences in type 1 and type 2 diabetes patients, the emotional issues patients have to deal with, such as self-management, worries about complications, and communicating about the disease, are highly
comparable. Therefore, we do not have reasons to believe that depression in type 1 and type 2 diabetes warrants different treatment. In our study, we also did not observe differences in the effectiveness of the intervention in type 1 or type 2 diabetes.

Future directions
The conclusions of this thesis provide directions for implementation of the intervention, and are is provided in this paragraph.

Furthermore, several issues raised in this thesis are worth studying in future research. These conclusions and recommendations for further research are also described in this paragraph.

The worldwide high prevalence of depression and diabetes stresses the importance of a diabetes-specific depression treatment. However, in comorbid psychological and somatic diseases, a central question is whether a disease-specific approach is merely more appealing to patients and has the potential to reduce stigma, or whether a disease-specific approach also adds to the effectiveness of an intervention. Therefore, it would be interesting to compare the effectiveness, feasibility and reach of a generic web-based CBT depression intervention with the diabetes-specific version.

Regarding the effectiveness of the intervention and bearing in mind the recurrent course of depression, the long-term effects of the web-based diabetes-specific CBT depression intervention on both psychological (e.g. depressive symptoms, diabetes-specific emotional distress) and diabetes outcomes (e.g. glycaemic control) are of great importance. Since we performed a waiting-list controlled trial, we will be able to study the pre-post effects of the intervention on depressive symptoms.

Since study attrition and intervention drop-out are both common features of both depression treatment and web-based interventions, future studies should explore strategies on how to reduce attrition and drop-out.

Since in our RCT, mainly relatively higher educated, Caucasian patients, with well-controlled diabetes enrolled themselves. Therefore, confirmation of the effectiveness of the intervention in relatively lower educated patients, ethnic minorities, and patients suffering from poorly controlled diabetes is required. Particularly in patients who suffer from severe complications from their diabetes, it might be that a specific approach is warranted to meet the needs of these specific subgroups of patients, e.g. an approach with a more central role for coping with physical disabilities.

Furthermore, it is of great importance that treatment itself is at least burdensome as possible. Therefore, patients’ evaluation of the web-based treatment is of great importance. Patients’ evaluation is also important for improving the intervention, e.g. making it more user-friendly.

Since chapter 3 pointed out that the relation between depression and glycaemic control is mediated by diabetes-specific emotional distress, it is of interest to compare the effectiveness in patients suffering from elevated diabetes-specific emotional distress compared with patients without distress.

Studying the cost-effectiveness of the intervention is of great importance and can be decisive in reimbursement.

Although not showing a direct effect on glycaemic control, it might be that the intervention did improve lifestyle behaviours and diabetes self-care behaviours.

Regarding the technological developments in society it is of great importance to keep the web-based intervention up to date to stay compatible with software and to keep an attractive, up to date character. Furthermore, the developments in the field of other technological devices, such as smart phones can provide other attractive opportunities for offering psychological interventions.
Implementation

Referral
Under detection (and subsequent under treatment) of depression in diabetes care is a common problem, caused by insufficient presentation of symptoms by patients, unstructured screening for depressive symptoms and trouble in distinguishing diabetes symptoms from depressive symptoms. The guidelines for diabetes care therefore recommend screening diabetes patients structurally for depression. However, screening for depression itself does not benefit depression; discussing the results of screening with patients and adequate referral to treatment are necessary to bring about beneficial effects.

Embedment in routine care
Now that the effectiveness of web-based diabetes-specific depression treatment has been demonstrated in adult type 1 and type 2 diabetes patients, implementation of the intervention into Dutch clinical practice seems the logical next step.

There are several thinkable options of implementation of the web-based diabetes-specific depression intervention in clinical practice. There are three plausible options for implementation of the intervention. First, since diabetes patients routinely visit the health care system for their diabetes care, this would offer the unique opportunity to detect depressive symptoms and refer patients to the intervention. Also, this would provide health care providers with a solution for referring their depressed patients. Second, in a mental health setting the intervention can be positioned in an approach for treatment of multiple morbidities. A third option is making the intervention freely accessible without embedment in routine primary, secondary or tertiary care, diabetes care or mental health care. A research grant from the Dutch National Action programme for Diabetes (NAD, see Chapter 1 General Introduction) enables us to study the optimal way of implementation of the intervention in diabetes care.

Considering the global problem of diabetes and depression and the ability to have a large reach, making the intervention available in other languages with the necessary cultural adaptations is of great importance, maximize the impact of the intervention. Replication of the study to examine the effectiveness of the culturally adapted versions of the intervention is then necessary. Currently, the intervention has been translated into English and plans are made on studying the effectiveness of this English version.

Concluding
For the first time, a web-based, diabetes-specific depression intervention has been developed. This thesis reflects on this intervention, its effectiveness, and its clinical implications. With support from the Dutch Diabetes Research Foundation, we were able to test the effectiveness of this intervention in a randomized, controlled trial. The intervention proved to be effective in reducing depressive symptoms and diabetes-specific emotional distress. This thesis can serve as a model for effectively addressing common co-occurring (mental) health problems via the Internet.
Summary

Web-based cognitive behaviour therapy for depression in adults with Type 1 or Type 2 diabetes

Chapter 1 provides the general introduction to the contents of this doctoral thesis. In summary, this chapter states that depression is a common comorbid health problem in adults with type 1 or type 2 diabetes mellitus. Depression is known to have serious adverse effects, not only on the quality of life of diabetes patients, but also on diabetes outcomes. Therefore, it is of great importance that depression in diabetes is adequately treated. Evidence suggests that treatment of depression in people with diabetes is both efficacious and cost effective and may result in improved overall diabetes control.

Addressing disease-specific emotional distress in depression treatment has been advised in previous studies, to increase effect sizes and to benefit the impact on diabetes outcomes. Using the internet to deliver psychological treatment can overcome isolation of time, mobility, and geography and thus increase reach and facilitate access to effective depression treatment, against relatively low costs. Primary aim of this thesis is to study the effectiveness of a web-based cognitive behavioural therapy (CBT) for adults with type 1 and type 2 diabetes in a randomised controlled trial (RCT). Secondary aims are to describe the design of the RCT, describe the development of the intervention, its reach and study whether its effectiveness differs for patients with more severe psychological problems compared with those with less severe problems. Furthermore, the relation between depressive symptoms, diabetes-specific emotional distress and glycaemic control has been studied in data from the baseline assessment of a depression in diabetes screening study carried out in three tertiary diabetes clinics in the Netherlands.

Chapter 2 describes the design of the randomised trial, which uses a wait-list control group. The intervention consists of an 8-week, moderated self-help course that is tailored to the needs of persons living with diabetes and is offered on an individual basis. Participants receive feedback on their homework assignments by e-mail from a personal coach, which is a medical or clinical psychologist. Power analyses showed that 286 patients (143/143) were needed to detect an effect size of 0.35. Measurements were performed at baseline, directly after completing the web-based intervention and at 1, 3, 4 and 6 months follow-up. Patients in the control condition were placed on a waiting list, and followed the course 12 weeks after randomisation. Primary outcomes were depressive symptoms, measured with the Centre for Epidemiologic Studies Depression Scale (CES-D). Secondary outcomes were diabetes-specific emotional distress, measured with the Problem Areas in Diabetes scale (PAID) and glycaemic control, indicated by glycosylated haemoglobin (HbA1c). All questionnaires were administered via the Internet.

Chapter 3 describes the study on diabetes-specific emotional distress that is hypothesized to mediate the relationship between depression and glycaemic control in patients with type 1 and type 2 diabetes. Data were derived from the baseline assessment of a depression in diabetes screening study carried out in three tertiary diabetes clinics in the Netherlands. Most recent glycosylated haemoglobin (HbA1c) measurement was obtained from medical records. The CES-D and PAID were used to measure depression and diabetes-specific emotional distress respectively. Linear regression was performed to examine the mediating effect of diabetes-distress. Complete data were available for 627 outpatients with type 1 (n = 280) and type 2 (n = 347) diabetes. Analyses showed that diabetes–distress mediated the relation between depression and glycaemic control and not differently for both disease types. From these results we conclude that in explaining the association between depression and
glycaemic control, diabetes-specific emotional distress appears to be an important mediator. Addressing diabetes-specific emotional problems as part of depression treatment in diabetes patients may help improve glycaemic outcomes.

Chapter 4 describes the development and reach of the web-based CBT programme for adults with type 1 and type 2 diabetes. Adding diabetes-specific topics to the effective online Dutch version of Lewinsohn’s Coping with Depression course resulted in a web-based CBT depression programme with incorporated diabetes-specific topics. The diabetes-specific topics were incorporated, based on advice from a diabetes patient panel and from health care professionals (diabetes nurse practitioner, a dietitian, and a medical psychologist) and using diabetes-specific topics from a CBT group programme for treatment of emotional distress in type 1 diabetes patients. The intervention consisted of an 8-lesson self-help course with minimal guidance by coaches, called www.diabetesthel.nl. Some examples of diabetes-specific topics that were incorporated in the course were: worrying about diabetes-specific complications, coping with reactions from environment on diabetes, and communicating with health care professionals. In the framework of a randomised trial, the intervention attracted serious interest of 540 diabetes patients. After screening, 255 diabetes patients were enrolled. Less than half had a history of depression treatment; 80% reported the diabetes-specific approach to be an important reason for signing up. A web-based diabetes-specific depression treatment was successfully developed. The programme attracting many diabetes patients who appreciate the diabetes-specific approach of the intervention, underscores the need for a depression intervention specifically tailored to diabetes patients.

Chapter 5 presents the results from the RCT in which the effectiveness of web-based CBT depression treatment in adults with type 1 and type 2 diabetes is being studied. The RCT was conducted in 255 adult diabetes patients with elevated depressive symptoms. The web-based CBT was effective in reducing depressive symptoms (with intention-to-treat analyses: \( P = 0.04, d = 0.29 \) and clinical improvement 41% vs. 24% \( P < 0.001 \); and per protocol analyses \( P < 0.001, d = 0.70, 56\% \) vs. 24% \( P < 0.001 \) at one month follow-up). Additionally, the intervention reduced diabetes-specific emotional distress \( (P = 0.03) \). We found no beneficial effect of the intervention on glycaemic control \( (P > 0.05) \), perhaps due to the study sample having relatively well-controlled diabetes. The web-based CBT depression treatment showed effective in reducing depressive symptoms in adults with type 1 and type 2 diabetes patients and additionally showed to reduce diabetes-specific emotional distress.

Chapter 6 presents finding from secondary analyses of the RCT. After the effectiveness of the web-based CBT was confirmed, a question that remained was whether the effectiveness differed for patients with seriously impaired mental health compared with patients with less severe mental health problems. Data of the RCT were used to test whether the effectiveness of web-based diabetes-specific CBT for depression differed in patients with and without diagnosed major depressive disorder (MDD), diagnosed anxiety disorder, or elevated diabetes-specific emotional distress (DM-distress). MDD, anxiety disorder, and elevated DM-distress showed to be no significant effect-modifiers.

The web-based diabetes-specific CBT depression treatment is therefore assumed to be suitable for use both in patients with severe mental health problems and in those with a less severe clinical profile.

Chapter 7 provides the general discussion of this thesis. In light of our results and previous research we can conclude that web-based CBT is an effective way of treating depression in type 1 and type 2 diabetes patients. Implications of the results, limitations of the study and future directions are being provided.
Nederlandse samenvatting

Cognitieve gedragstherapie via het internet voor depressie in volwassenen met diabetes type 1 of type 2

Hoofdstuk 1 is een algemene inleiding van de inhoud van dit proefschrift. Kort samengevat wordt in dit hoofdstuk beschreven dat depressie een veelvoorkomende comorbiditeit is in volwassenen met diabetes mellitus type 1 of type 2. Het is bekend dat depressie een ernstige negatieve invloed heeft, niet alleen op de kwaliteit van leven van diabetespatiënten, maar ook op de diabetes uitkomsten. Daarom is het van groot belang dat depressie in diabetes adequaat behandeld wordt. Wetenschappelijk onderzoek heeft laten zien dat behandeling van depressie bij diabetespatiënten zowel effectief als ook kosteneffectief is en dat het kan resulteren in verbetering van diabetesuitkomsten. Het behandelen van diabetesgerelateerde emotionele klachten in depressie behandeling bij diabetespatiënten is in vorige studies aangeraden, omdat dit mogelijk resultert in grotere behandel effecten en grotere effecten op diabetesuitkomsten. Het gebruik van het internet om psychologische interventies aan te bieden kan drempels qua tijd, mobiliteit en geografische afstand overbruggen en zodoende de toegankelijkheid tot depressie behandeling vergroten en daarmee het bereik vergroten, tegen lagere kosten. Het primaire doel van dit proefschrift is om de effectiviteit te bestuderen van cognitieve gedragstherapie (CGT) voor de behandeling van depressie via het internet voor volwassenen met diabetes type 1 en type 2 in een gerandomiseerde controloeraerde studie (RCT). Het secundaire doel is om het design van de RCT te beschrijven, de ontwikkeling van de interventie en zijn bereik en bestuderen of zijn effectiviteit verschilt in patiënten met ernstigere psychologische problemen vergeleken met minder ernstige psychische problemen. Daarnaast, is de relatie tussen depressieve klachten, diabetes specifieke emotionele klachten en glykemische instelling bestudeerd in data van de baseline meting van een depressie in diabetes screening studie, die uitgevoerd is in drie tertiaire zorg diabetes klinieken in Nederland.

Hoofdstuk 2 beschrijft het design van de wachtlijst gecontroleerde, gerandomiseerde studie, waarin de effectiviteit van CGT voor de behandeling van depressie via het internet voor volwassenen met diabetes type 1 en type 2 wordt onderzocht. De interventie bestaat uit een 8-weekse, begeleide zelfhulp cursus die is aangepast aan de behoefte van mensen die met diabetes leven en wordt aangeboden op individueel niveau. Deelnemers ontvangen feedback op hun huiswerkopdrachten per e-mail van een persoonlijke coach, die een medisch of klinisch psycholoog is. De poweranalyse liet zien dat 286 (143 / 143) patiënten nodig waren om een effectgrootte van 0.35 aan te kunnen tonen. Er werden metingen verricht op baseline, direct na het voltooien van de interventie en 1, 3, 4 en 6 maanden later. Patiënten in de controlegroep werden op een wachtlijst geplaatst en volgden de cursus 12 weken na randomisatie. Primaire uitkomsten waren depressieve symptomen, gemeten met de CES-D vragenlijst. Secundaire uitkomstmaat was diabetes specifieke emotionele klachten, gemeten met de PAID en glykemische controle, aangeduid met HbA1c die opgevraagd waren bij de behandeldelv. Alle vragenlijsten zijn afgenomen via het internet.

Hoofdstuk 3 beschrijft de studie naar diabetes specifieke emotionele klachten, waarvan verwacht wordt dat deze de relatie tussen depressie en glykemische controle medeert in mensen met diabetes type 1 en 2. Data zijn afkomstig van de baseline meting van een depressie in diabetes screening studie die uitgevoerd is in drie diabetes klinieken in Nederland. De meest recente HbA1c-metingen zijn uit medische dossiers gehaald. De CES-D en de PAID zijn gebruikt om depressie en diabetes specifieke emotionele klachten te meten. Lineaire regressie is uitgevoerd om het mediërende
effect te onderzoeken. Volledige data waren beschikbaar van 627 poliklinische patiënten met diabetes type 1 (n = 280) en type 2 (n = 347). Analyses lieten zien dat emotionele klachten van diabetes de relatie tussen depressie en glykemische controle verbeterden, onverschillig voor de twee types diabetes. Uit deze resultaten concludeerden we dat in het verklaren van de relatie tussen depressie en glykemische controle, diabetespecifieke emotionele klachten een belangrijke mediator blijken te zijn. Het aanpakken van diabetespecifieke emotionele klachten in depressiebehandeling van diabetespatiënten zou daarom kunnen helpen bij het verbeteren van glykemische uitkomsten.

Hoofdstuk 4 beschrijft de ontwikkeling en het bereik van het CGT programma. Het toevoegen van diabetespecifieke onderwerpen aan de effectieve online Nederlandse versie van Lewinsohn’s Coping with Depression course (in Nederland heet deze cursus “In the put, uit de put”) resulteerde in een online CGT depressie programma, met ingebouwde diabetespecifieke onderwerpen. De diabetespecifieke onderwerpen zijn toegevoegd op basis van advies van een diabetes patiëntenpanel en van gezondheidszorg professionals (bijv. Diabetesverpleegkundige, medisch psycholoog) en door onderwerpen te gebruiken uit een CGT groepsprogramma voor de behandeling van emotionele klachten in patiënten met diabetes type 1. De interventie, genaamd Diabetergestemd.nl, bestond uit een zelfhulp cursus met 8 lessen en met minimale begeleiding van een coach. Enkele voorbeelden van diabetespecifieke onderwerpen die in de cursus aan bod kwamen zijn: plekken over diabetespecifieke complicaties, omgaan met reacties uit je omgeving op diabetes en communiceren met hulpverleners. In het kader van een RCT, hebben 540 diabetespatiënten interesse in de interventie getoond. Na screening zijn 255 diabetespatiënten geïncludeerd in de studie. Minder dan de helft had in het verleden behandeling gehad voor depressie; 80% rapporteerde dat de diabetespecifieke benadering een belangrijke reden was om zich aan te melden. Concluderend is een diabetespecifieke internettherapie voor depressie succesvol ontwikkeld. Het programma heeft veel mensen met diabetes aangetrokken die de diabetespecifieke benadering waarderen, wat het belang van een depressie-interventie specifiek voor diabetespatiënten onderstrept.

Hoofdstuk 5 presenteert de resultaten van de RCT waarin de effectiviteit van online CGT voor de behandeling van depressie voor volwassenen met diabetes type 1 en type 2 wordt onderzocht. De RCT is uitgevoerd onder 255 diabetespatiënten met verhoogde depressieve klachten. Diabetergestemd.nl bleek effectief in het doen reduceren van depressieve klachten (met intention-to-treat analyses: P = 0.04, d = 0.29 en klinisch relevante verbetering 41% vs. 24% P <0.001; en per protocol analyses P <0.001, d = 0.70, 56% vs. 24% P <0.001 op de één maand follow-up meting). Aanvullend bleek de interventie diabetespecifieke emotionele klachten te reduceren (P = 0.03). We vonden geen effect van de interventie op glykemische controle (P > 0.05), wat mogelijk verklaard kan worden doordat de deelnemers op baseline relatief goed ingesteld waren. Concluderend laat hoofdstuk 5 zien dat de internetinterventie effectief is in het doen reduceren van depressieve klachten in volwassenen met diabetes type 1 of type 2 en in het doen reduceren van diabetespecifieke emotionele klachten.

Hoofdstuk 6 presenteert de bevindingen van een secundaire analyse op de data van de RCT. Nadat de effectiviteit van Diabetergestemd.nl was bevestigd, was een vraag die restte of deze effectiviteit mogelijk verschilde voor patiënten met meer ernstige psychische klachten in vergelijking tot patiënten met minder ernstige psychische problemen. Data van de RCT zijn gebruikt om te onderzoeken of de effectiviteit van Diabetergestemd.nl verschilde voor patiënten met dan wel zonder een gediagnosticeerd depressie (major depressive disorder, MDD), een gediagnosticeerde angststoornis en diabetespecifieke emotionele klachten. MDD, angststoornis en
diabetesspecifieke emotionele klachten bleken geen significante effect-modificatoren. Diabetergestem.nl is daarom aannemelijk geschikt voor gebruik bij mensen met en zonder ernstige psychische problemen.

Hoofdstuk 7 biedt tot slot een algemene discussie van dit proefschrift. In het licht van de resultaten beschreven in dit proefschrift en voorgaand onderzoek kunnen we concluderen dat CGT via het internet een effectieve manier is van het behandelen van depressie in patiënten met diabetes type 1 en type 2. Een samenvatting en interpretatie van de onderzoeksresultaten, krachten en kanttekeningen van/bij het onderzoek en aanwijzingen voor de toekomst worden in dit laatste hoofdstuk verschafte.
References


References


107. Glasgow RE, Barrera M, Jr., McKay HG, Boles SM: Social support, self-management, and quality of life among participants in an internet-based...


157. Snoek FJ, van d, V, Twisk JW, Hogenest MH, Tromp-Wever AM, van der Ploeg HM, Heine RJ: Cognitive behavioural therapy (CBT) compared with blood glucose awareness training (BGAT) in poorly controlled Type 1 diabetic


168. Cuijpers P: Review: relaxation better than wait-list, minimal or no treatment for depression but not as good as psychological treatments. *Evid Based Ment Health* 12:76-77, 2009


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