

Web-Based Depression Treatment for Type 1 and Type 2 Diabetic Patients

A randomized, controlled trial

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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). The Internet is a new and attractive method for delivering CBT intervention on a large scale at relatively low costs. This study evaluated 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 the Netherlands in 255 adult diabetic patients with elevated depressive symptoms. Primary outcomes were depressive symptoms. Secondary outcomes were diabetes-specific emotional distress and glycemic control. Assessments were at baseline, after treatment, and at the 1-month follow-up.

RESULTS—The Web-based CBT was effective in reducing depressive symptoms by intention-to-treat analyses ($P = 0.04$, $d = 0.29$; clinical improvement 41% vs. 24% $P < 0.001$) and by per-protocol analyses ($P < 0.001$, $d = 0.70$; clinical improvement, 56% vs. 24% $P < 0.001$). The intervention reduced diabetes-specific emotional distress ($P = 0.03$) but had no beneficial effect 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. In addition, the intervention reduces diabetes-specific emotional distress in depressed patients.

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Affecting 10 to 20% of adult diabetic patients, depression is a common comorbid health problem among people with type 1 or type 2 diabetes (1). 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 (2). 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 (2). 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 (2).

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 (3). 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 (4).

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 (5). The effectiveness of a Web-based version of CWD—Color Your Life (CYL)—has been shown (6,7). 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 (5).

Between 56 and 75% of depressed patients with diabetes experience high levels of emotional distress directly related to diabetes (8). Recent studies have shown that the beneficial effects of depression treatment on glycemic control are mediated by diabetes-related distress (9,10). 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 (9).

Therefore, in close collaboration with the researchers who developed CYL, we adapted this course to meet the needs of diabetic patients, thus maximizing acceptability (11). This diabetes-sensitive CYL (Diabetergestemd.nl, 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 (11).

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

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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

This 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 (12). 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 (Fig. 1).

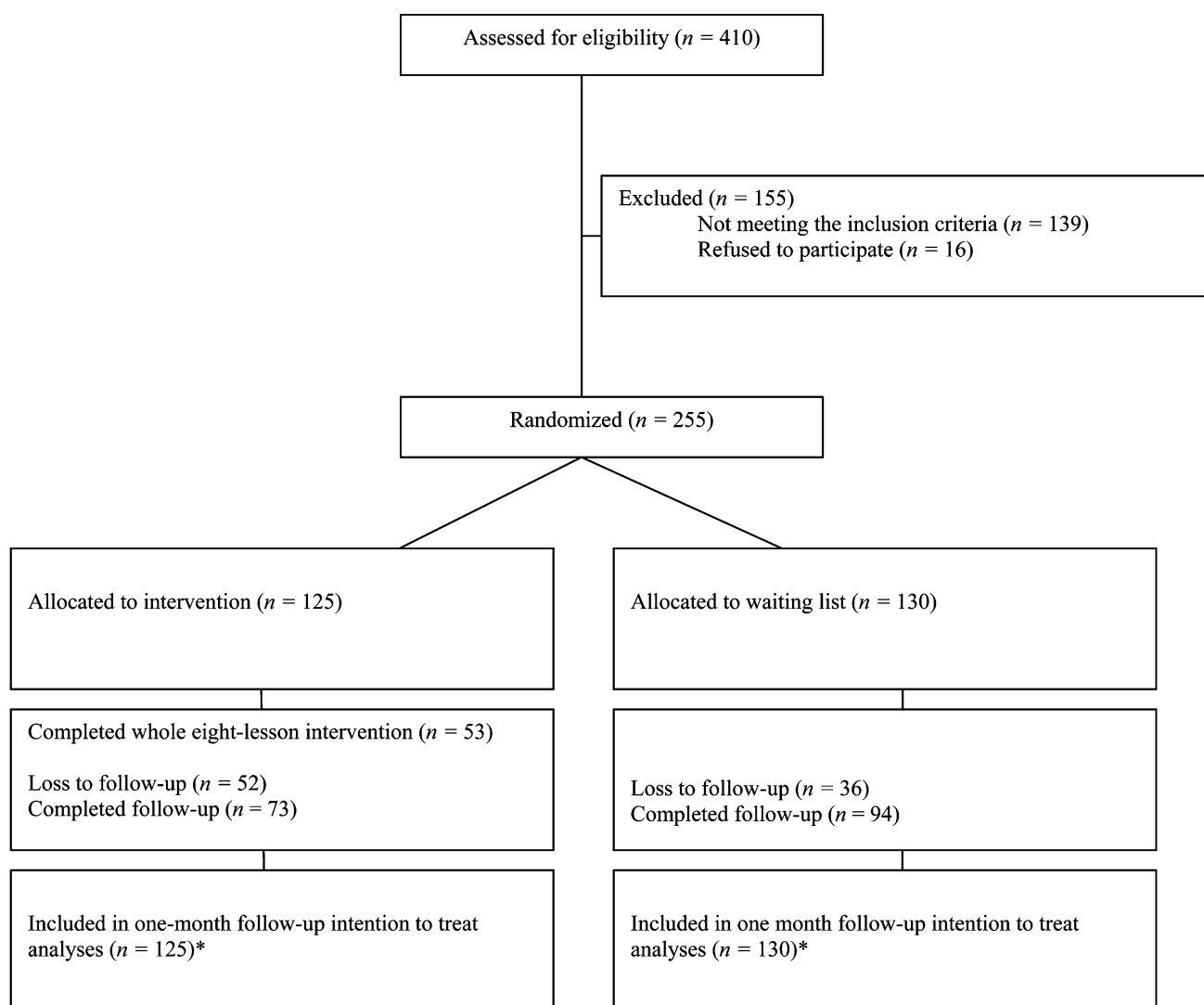
Setting and participants

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



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

Figure 1—Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

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 CBT. A detailed description of the intervention can be found elsewhere (11). In short, participants individually went through eight consecutive lessons that provided written and spoken information and videos of depressed diabetic 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 (postassessment) 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).

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 of Mental Disorders* (DSM-IV) (13). Because 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 (14). 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 (15). 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 (8,15).

As an indicator of glycemic control, patients’ glycosylated hemoglobin (A1C, 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 A1C of $\geq 8\%$ (16).

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 α of 0.05, 100 subjects were required in each group to be able to detect differences with an effect size of 0.35 (17). 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, χ^2 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 DG.nl were compared with the control group.

Longitudinal regression analyses were performed using generalized estimating equations. Interaction effects of treatment (intervention versus control group) \times 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 post-treatment 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: $d = M_1 - M_2 / \sigma_{\text{pooled}}$, in which $\sigma_{\text{pooled}} = \sqrt{[(\sigma_1^2 + \sigma_2^2) / 2]}$.

Effect sizes larger than $d = 0.8$ were considered to be large, $d = 0.5$ – 0.8 as moderate, and $d = 0.2$ – 0.5 as small (18).

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 (14). Improvement was determined following the suggestions of Jacobson and Truax (19), calculating a reliable change index (RC) using the following formula: $RC = (x_2 - x_1) / s_{\text{diff}}$. Patients who both improved and recovered were considered as being “clinically significantly improved.”

Learning from previous studies on Web-based interventions, we expected high study attrition rates (4). 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 (20). 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 ($P < 0.01$; Fig. 1).

Regarding the intervention group, study attrition was higher in noncompleters of the course at the 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 (20).

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 A1C was $7.4 \pm 1.3\%$, indicating relatively well-controlled diabetes, with 27% having an elevated level of A1C ($>8.0\%$). Seventy-nine patients (31%) self-reported one or more diabetes complication.

Table 1—Baseline sociodemographic and clinical characteristics of participants at baseline

Characteristics	All patients ($n = 255$)	CBT participants ($n = 125$)	Waiting list control* ($n = 130$)
Sociodemographics			
Mean age, year	50 ± 12	48 ± 12	51 ± 12
Women, n (%)	155 (61)	82 (66)	73 (56)
Caucasian, n (%)	227 (89)	110 (88)	117 (90)
Marital state—with partner, n (%)	199 (78)	99 (79)	100 (77)
Education level, n (%)			
No formal qualifications	8 (4)	5 (5)	3 (3)
High school or lower/middle vocational qualifications	136 (53)	70 (56)	66 (51)
College qualifications or more	111 (44)	50 (40)	61 (47)
Employed, n (%)	126 (49)	64 (51)	62 (48)
Lifestyle-related factors			
Smoking, n (%)	45 (18)	23 (18)	22 (17)
Mean alcohol consumption, units/week	6 ± 7	5 ± 7	7 ± 8
Clinical diabetes profile			
Type 2 diabetes, n (%)	141 (55)	66 (53)	75 (58)
Insulin-treated type 2, n (%)	69 (49)	35 (53)	34 (45)
Mean duration of diabetes in type 1, year	21 ± 13	20 ± 12	22 ± 15
Mean duration of diabetes in type 2, year	9 ± 8	8 ± 8	9 ± 9
Mean BMI	28 ± 5	27 ± 5	28 ± 5
Mean A1C level, %	7.4 ± 1.3	7.4 ± 1.6	7.3 ± 1.6
Diabetes complications, n (%)			
Neuropathy	25 (10)	11 (9)	14 (11)
Nephropathy	11 (4)	5 (4)	6 (5)
Retinopathy	30 (12)	17 (14)	13 (10)
Foot ulcers	21 (8)	9 (7)	12 (9)
Mean depressive symptoms: CES-D (range 16–60)	28 ± 7	29 ± 7	28 ± 7
Diagnosed with MDD (WHO CIDI), n (%)	146 (57)	71 (57)	75 (58)
Current antidepressive medication use, n (%)	28 (11)	14 (11)	14 (11)
Mean diabetes-specific emotional distress: PAID (range 0–100)	40 ± 19	42 ± 19	38 ± 19

Data are expressed as mean \pm 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 sociodemographic or clinical baseline characteristics.

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 noncompleters. Generalized estimating equation analyses revealed a significant treatment multiplied 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 A1C levels ($P > 0.05$). When patients with elevated baseline A1C levels only were examined, a significant treatment

effect was still not found for A1C ($P > 0.05$).

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%, $P < 0.001$).

PP 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 during the course. The 53 completers and the 72 noncompleters

of the course did not significantly differ on any of the measured baseline characteristics.

Stronger 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 significantly 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 individuals with 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 (21).

Furthermore, our method of recruiting participants through a freely accessible Web site could have led toward 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 (22). 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 having “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 A1C 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 be 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 (23,24). 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 (25). 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.

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