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ORIGINAL ARTICLE

Effects of a transdiagnostic unguided Internet intervention ('velibra') for anxiety disorders in primary care: results of a randomized controlled trial

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Background. Internet-based cognitive–behavioural treatment (ICBT) for anxiety disorders has shown some promise, but no study has yet examined unguided ICBT in primary care. This randomized controlled trial (RCT) investigated whether a transdiagnostic, unguided ICBT programme for anxiety disorders is effective in primary care settings, after a face-to-face consultation with a physician (MD). We hypothesized that care as usual (CAU) plus unguided ICBT would be superior to CAU in reducing anxiety and related symptoms among patients with social anxiety disorder (SAD), panic disorder with or without agoraphobia (PDA) and/or generalized anxiety disorder (GAD).

Method. Adults ($n = 139$) with at least one of these anxiety disorders, as reported by their MD and confirmed by a structured diagnostic interview, were randomized. Unguided ICBT was provided by a novel transdiagnostic ICBT programme ('velibra'). Primary outcomes were generic measures, such as anxiety and depression symptom severity, and diagnostic status at post-treatment (9 weeks). Secondary outcomes included anxiety disorder-specific measures, quality of life, treatment adherence, satisfaction, and general psychiatric symptomatology at follow-up (6 months after randomization).

Results. CAU plus unguided ICBT was more effective than CAU at post-treatment, with small to medium between-group effect sizes on primary (Cohen's $d = 0.41$–0.47) and secondary (Cohen's $d = 0.16$–0.61) outcomes. Treatment gains were maintained at follow-up. In the treatment group, 28.2% of those with a SAD diagnosis, 38.3% with a PDA diagnosis, and 44.8% with a GAD diagnosis at pretreatment no longer fulfilled diagnostic criteria at post-treatment.

Conclusions. The unguided ICBT intervention examined is effective for anxiety disorders when delivered in primary care.

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Key words: Anxiety, cognitive–behaviour therapy, Internet, primary care, transdiagnostic treatments.

Introduction

Anxiety disorders are common and associated with substantial disability (Kessler *et al.* 1994; Mendlowicz & Stein, 2000). General practitioners (GPs) are usually the first professional contact for patients with anxiety disorders (Bijl & Ravelli, 2000; Wang *et al.* 2007). However, only a minority of diagnosable cases is identified as such in primary care (Kessler *et al.* 1999; Löwe *et al.* 2003), and when recognized, only few patients are referred to specialized mental health care (Wang *et al.* 2007). Patients with anxiety disorders are thus likely to receive their only treatment from general medical providers (Regier *et al.* 1993; Katz *et al.* 1998), which is in most cases pharmacotherapy (Weiller *et al.* 1998; Wang *et al.* 2002). Although medication can be an effective treatment option (Baldwin *et al.* 2005), many patients do not receive psychotropic medication at an appropriate dose and for an appropriate duration (Stein *et al.* 2004). Moreover, many patients prefer psychological therapies (van Schaik *et al.* 2004). Evidence-based psychotherapies, such as cognitive–behavioural therapy (CBT), are at least as effective as pharmacotherapy and should be considered, especially if initial treatment with medications proves inadequate (Issakidis *et al.* 2004; Butler *et al.* 2006).

General medical providers often lack resources and training necessary to provide evidence-based psychological treatments. One way of increasing access to

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evidence-based psychological treatment in primary care is Internet-based cognitive–behavioural treatment (ICBT). ICBT has been shown to be effective for a variety of anxiety and mood disorders (Andersson, 2016). Most of the growing body of evidence comes from studies evaluating guided self-help treatments. While patients work their way through a modularized, CBT-based self-help programme, therapists assist them, for example, via a secured email system. Several meta-analyses suggest that guided treatments lead to better outcomes than unguided treatments (Spek *et al.* 2007; Richards & Richardson, 2012). However, especially in the field of anxiety disorders, good outcomes have also been reported in trials of unguided ICBT (Berger *et al.* 2011*a*; Dear *et al.* 2015).

Given that the efficacy of ICBT has been established, in principle, an important new area of investigation is practice-oriented research on how this knowledge can be applied to routine health care (Emmelkamp *et al.* 2014). In recent years, a series of studies has evaluated the effectiveness of ICBT for anxiety disorders when delivered in psychiatric settings (Aydos *et al.* 2009; Bergstrom *et al.* 2010; Andrews *et al.* 2011; Hedman *et al.* 2011; Ruwaard *et al.* 2012; Hedman *et al.* 2013; El Alaoui *et al.* 2015; Titov *et al.* 2015) and a few trials have investigated ICBT in primary care settings (Newby *et al.* 2013; Williams & Andrews, 2013; Newby *et al.* 2014; Nordgren *et al.* 2014). In those studies conducted in primary care, participants were recruited through their primary care contact and were supported either by the primary care practitioner or by therapists associated with the study team. The current study aimed to extend this work by investigating whether unguided ICBT for anxiety disorders is effective when delivered after a contact with a physician (MD), usually a GP. This form of dissemination may be representative because many physicians may lack the time to provide regular ICBT support in routine practice. For most practising physicians, it might be more feasible to prescribe unguided treatments after an initial examination and then conduct routine symptom monitoring, rather than provide intensive support for ICBT.

In contrast to previous studies, participants in this trial were recruited not only through their primary care contact but were also allowed to initiate participation by themselves (e.g. when they heard about the study through other channels, such as our study website or newspaper articles). In the latter case, participants were asked to inform their MD about their desire to participate in the study, to provide him or her with an information sheet, and to let the MD prescribe ICBT after a required face-to-face consultation. We combined the possibility of self-referral with the requirement of an MD consultation for safety reasons and because individuals increasingly obtain (mental) health information through the Internet prior to or in parallel with seeing their physician (Ball & Lillis, 2001). Patients are thus increasingly likely to gain knowledge and develop preferences about available treatments independently from their physicians. Consequently, the patient-initiated use of ICBT after a consultation with a medical professional may become a common delivery model of ICBT in primary care.

We evaluated a novel transdiagnostic and tailored programme that targeted several anxiety disorders, namely social anxiety disorder (SAD), panic disorder with or without agoraphobia (PDA) and generalized anxiety disorder (GAD). Although most of the evidence on ICBT comes from studies evaluating disorder-specific treatments, alternative treatment approaches have emerged with the aim of simultaneously treating both primary and co-morbid disorders (Titov *et al.* 2010; Carlbring *et al.* 2011). Both tailored ICBT, which modifies the treatment according to patient symptom characteristics and co-morbidities, and transdiagnostic ICBT, which is designed to target common underlying symptoms and predisposing psychological factors for anxiety and depression (Barlow *et al.* 2004), have yielded promising results (Titov *et al.* 2010; Carlbring *et al.* 2011). Although transdiagnostic and tailored approaches may not be more effective than disorder-specific treatments (Berger *et al.* 2014; Dear *et al.* 2015; Fogliati *et al.* 2016), they have other advantages, particularly when delivered in primary care. An important pragmatic advantage is that transdiagnostic and tailored treatments address a broader range of patients. Moreover, the transdiagnostic approach requires treatment providers to manage only one rather than several online programmes and reduces the importance of properly coding a single principal diagnosis, particularly when symptoms of several anxiety disorders are simultaneously present, which is common (Kroenke *et al.* 2007). These pragmatic advantages seem especially important when considering the low detection rate of anxiety disorders in primary care (Kroenke *et al.* 2007).

In order to evaluate whether an unguided, transdiagnostic ICBT intervention for several anxiety disorders can be effective when delivered after a consultation with an MD, we conducted a randomized controlled trial (RCT). The intervention plus care as usual (CAU) was compared with a CAU control condition among participants fulfilling the diagnostic criteria of at least one of these anxiety disorders. To our knowledge, this is the first study of a transdiagnostic unguided treatment for anxiety disorders conducted in a primary care setting. We hypothesized that the 9-week intervention, offered adjunctively to CAU,

would be superior to CAU alone in reducing anxiety and related symptoms, such as depression.

Method

Study design

This RCT compared an immediate treatment group with an active waiting-list control group. Both groups had access to CAU. The waiting-list control group was enrolled in the ICBT programme after the treatment group had completed the programme (after 9 weeks). The immediate treatment group was followed up until 6 months after randomization to examine the stability of potential treatment gains. We aimed at detecting a standardized between-group effect size (Cohen's d) of 0.35. Smaller effect sizes were considered to be irrelevant from a clinical point of view. A power analysis revealed that at an α error level of 0.05 and power ($1 - \beta$) of 0.80, approximately 88 participants per group would be required to detect a small to medium effect (Cohen's $d = 0.35$).

Participants

The participation in the study required an MD, usually a GP, to send us a signed document stating that (1) the MD had seen the patient, (2) the MD confirmed a SAD, PDA and/or GAD diagnosis, and (3) there were no medical reasons or other objections against the patient's participation in the study. The specific recruitment process differed among participants. While some participants first heard about the study from their MD (some MDs in Germany and Switzerland had been informed about the study), most participants first visited our study website (www.online-therapy.ch), then consulted an MD and asked him or her to sign and postmark the necessary document to participate in the study. Participants were recruited in Switzerland, Germany and Austria. After returning a written informed consent form signed by the participant and the signed document from the MD, participants were asked to complete online versions of the outcome measure questionnaires. Questions concerning demographic variables, previous or ongoing psychological treatment, and prescribed medication for depression/anxiety were included as well. After completing the questionnaires, participants were interviewed by telephone using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) Axis I disorders (SCID; First *et al.* 1995). Five advanced masters students in clinical psychology and psychotherapy, three doctoral-level students in clinical psychology and psychotherapy, and the first author (T.B.) conducted the interviews. All SCID interviewers were trained in several sessions using the SCID manual and sample interviews. Additional supervision by the first author (T.B.) was provided throughout the study.

Criteria for inclusion were (*a*) age of at least 18 years, (*b*) access to the Internet, (*c*) sufficient knowledge of the German language, (*d*) a primary diagnosis of SAD, PDA or GDA as indicated by the MD and confirmed by the SCID, (*e*) no history of a psychotic or bipolar disorder, and (*f*) if taking prescribed medication for depression/anxiety, the dosage had to be constant for at least 1 month before the start of the treatment. Individuals indicating suicidal ideation with intent in the diagnostic interview would have been excluded and referred to the GP or a local psychiatrist. However, no participant reported suicidality in the interview.

Details of the participant flow are shown in Fig. 1. A total of 40 applicants were excluded after providing informed consent but prior to randomization, mainly because they did not fulfill the diagnostic criteria of one of the anxiety disorders ($n = 22$) or because they were not reached for the SCID ($n = 9$). A total of 139 participants met all inclusion and none of the exclusion criteria and were thus randomized to one of the two conditions. A stratified randomization procedure was applied, such that a balanced distribution of primary diagnosis, medication and concurrent psychotherapy in the two conditions was ensured. The allocation lists were made using a computerized random number generator and were concealed from the investigators and participants. After the randomization, the participants received an automated email regarding their group allocation. In case they were allocated to the treatment group, an access code to the velibra programme and a description of how to access it were provided. After 9 weeks, all participants were requested to complete post-treatment questionnaires via the Internet, and to take part in a post-treatment telephone interview, in which the relevant SCID-I modules were re-evaluated. At this time, control group participants also received access to velibra. At 6 months after randomization (i.e. about 4 months after post-treatment), participants were contacted via email and asked to complete the questionnaires again. The protocol of this study was approved by the Ethics Committee of the Canton of Bern, and the trial was registered at www.controlled-trials.com (ISRCTN81412545).

Primary outcome measures

Participants completed self-report measures at pre-treatment, post-treatment (9 weeks) and follow-up (6 months after randomization). All questionnaires were administered via the Internet. Because not all participants suffered from the same primary disorder, disorder-

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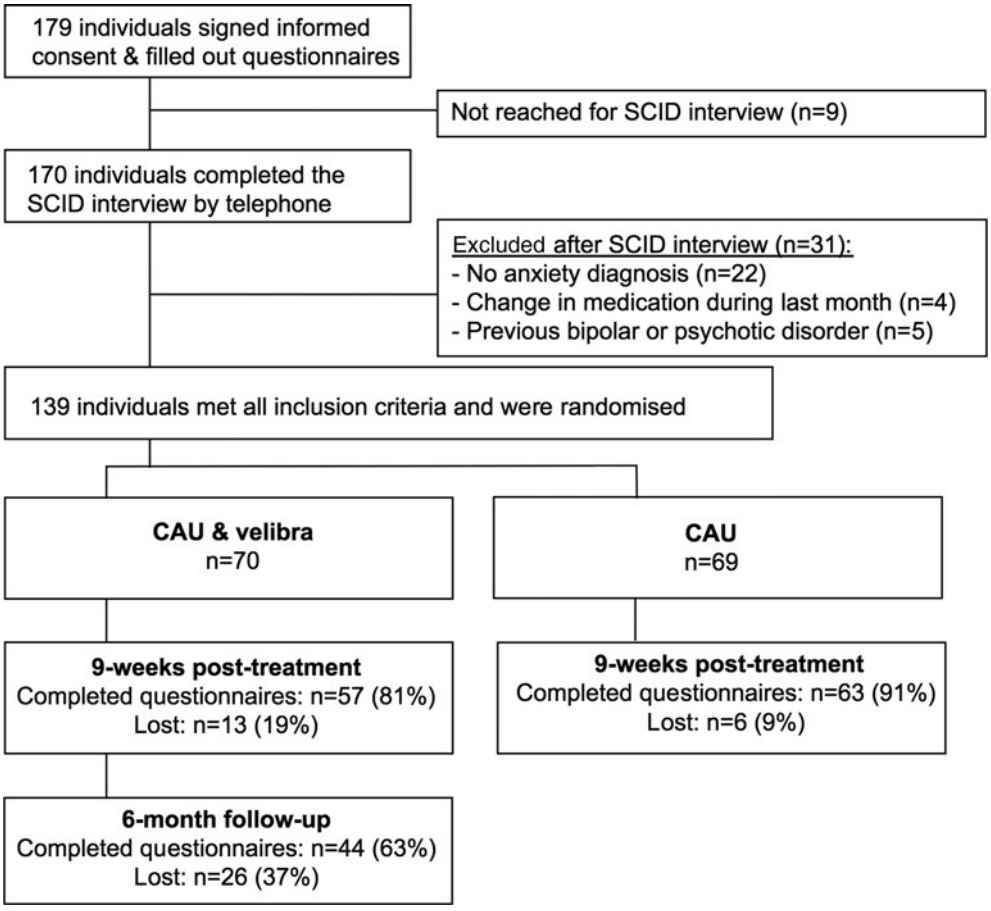

Fig. 1. Selection, randomization and flow of participants through the trial. SCID, Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) Axis I disorders; CAU, care as usual.

unspecific measures such as the Depression Anxiety Stress Scales – Short Form (DASS-21; Lovibond & Lovibond, 1995), the Beck Anxiety Inventory (BAI; Beck *et al.* 1988), the Beck Depression Inventory-II (BDI-II; Beck *et al.* 1996), the Brief Symptom Inventory (BSI; Derogatis, 1993) and the Short-Form Health Survey-12 (SF-12; Ware *et al.* 1996) were used as primary outcome measures. The DASS-21 measures depression, anxiety and tension/stress. We only report results for the composite measure of the DASS-21. In the current sample, Cronbach's α for the composite scale was 0.90. The 21-item BAI was included as a general measure of anxiety-related symptoms across disorders (Cronbach's $\alpha = 0.75$). The BDI-II was used to assess current depressive symptoms (Cronbach's $\alpha = 0.89$). General psychopathology was measured with the BSI. For the purpose of this study, the Global Severity Index (GSI) was used (Cronbach's $\alpha = 0.93$). To measure quality of life, we used the SF-12. Its two subscales measure physical and mental aspects of health-related quality of life. The test–retest reliability of this 12-item measure is good, roughly equivalent to the long-form (Ware *et al.* 1996).

In addition to the self-report measures a diagnostic interview was conducted at pre- and post-treatment. At post-treatment, the interviewers only administered the diagnostic modules of the SCID-I for which participants had fulfilled the diagnostic criteria in the pre-treatment interview. The interviewers could not be kept blind at post-assessment regarding group assignment.

Secondary outcome measures

Disorder-specific instruments were used as secondary outcome measures. To measure social anxiety symptoms, we used the Social Phobia Scale (SPS) and the Social Interaction Anxiety Scale (SIAS; Mattick & Clarke, 1998). The 20-item SPS and the 20-item SIAS were designed as companion measures, the former focusing on fear of scrutiny and evaluation, the latter concentrating on interaction anxiety. The internal reliabilities in the current sample were $\alpha = 0.93$ for the SPS and $\alpha = 0.94$ for the SIAS. The 14-item Agoraphobic Cognitions Questionnaire (ACQ; Chambless *et al.* 1984) was used

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Table 1. *Content of the six sessions in velibra*

Session 1: Introduction	Explaining the programme's purpose and function; psychoeducation regarding the aetiology and maintenance of anxiety; introduction to a CBT approach; identifying symptom focus (e.g. GAD, SAD, PD); exploring treatment motivation
Session 2: Coping with anxiety-related cognitions	Understanding and identifying automatic thoughts and cognitive distortions (e.g. catastrophizing); learning to challenge or distance oneself from unhelpful thoughts
Session 3: Learning mindfulness and relaxation exercises	Rationale for using mindfulness and relaxation exercises, introducing and practising specific exercises, including breathing, mental imagery and muscle relaxation exercises
Session 4: Understanding and practising exposure	General and disorder-specific explanations of the role of exposure in anxiety treatment; disorder-specific examples and instructions for self-guided exposure exercises (e.g. worry exposure in GAD, interoceptive exposure in PD, social situations in SAD), in-depth explanation and examples of approach *v.* avoidance behaviour and their respective functions in anxiety
Session 5: Social skills, social support and interpersonal relationships	Exploring the quality of the user's social support network, suggestions for improving interpersonal relationships, discussions on specific anxiety-related social situations (e.g. giving a presentation)
Session 6: Summary and relapse prevention	Quiz to review and test anxiety-related knowledge, review of selected key principles (acceptance, approach focus, self-compassion), illustrated case story to reiterate core principles

CBT, Cognitive–behavioural therapy; GAD, generalized anxiety disorder; SAD, social anxiety disorder; PD, panic disorder.

to measure cognitions regarding the catastrophic consequences of experiencing panic (Cronbach's $\alpha = 0.79$). To measure fear of body sensations, we used the 17-item Body Sensations Questionnaire (BSQ; Chambless *et al.* 1984; Cronbach's $\alpha = 0.89$). Agoraphobic avoidance was assessed using the Mobility Inventory for Agoraphobia (Chambless *et al.* 1985), which consists of the two subscales 'avoidance alone' (MIA; Cronbach's $\alpha = 0.96$) and 'avoidance accompanied' (MIB; Cronbach's $\alpha = 0.96$). The 16-item Penn State Worry Questionnaire (PSWQ; Meyer *et al.* 1990) was used to capture the generality, excessiveness and uncontrollability of pathological worry (Cronbach's $\alpha = 0.87$). At post-treatment, a measure of global patient satisfaction was also administered (Client Satisfaction Questionnaire; CSQ-8; Attkisson & Zwick, 1982).

Description of treatment

Participants in the intervention group received access to the self-help programme 'velibra', which was developed by Gaia AG, Hamburg, Germany, an e-Health company that has developed several previous Internet interventions, including 'deprexis', a depression-focused programme that has been tested in several RCTs (e.g. Meyer *et al.* 2009; Berger *et al.* 2011*b*; Moritz *et al.* 2012; Klein *et al.* 2016). Velibra consists of six treatment modules, the first five of which are followed by a 'training session', containing exercises addressing cognitive bias modification for interpretation (CBM-I; Beard & Amir, 2008). The six treatment modules are cognitive–behavioural in orientation and emphasize transdiagnostic principles, such as anxiety as an evolutionary adaptive emotion, the 'false alarm' model of anxiety, experiential avoidance, and the role of approach *v.* avoidance motivation (Mogg & Bradley, 1998; Carver, 2006; Grawe, 2007; Barlow *et al.* 2010; McManus *et al.* 2010; Bateson *et al.* 2011). Table 1 describes the content of the six modules. In velibra, content is conveyed via brief text passages, illustrations, audio recordings, downloadable PDF documents (summaries, worksheets), and daily fully automated text messages, which can be received as SMS (short message service) (optionally) or emails. The programme also contains several 'symptom tracking' questionnaires, allowing users to self-monitor changes in symptom severity. Users generally navigate the programme by reading brief text passages and continuously selecting response options deemed most relevant. Because the programme adjusts subsequent content based on individual responses, an 'individually tailored dialogue' emerges between programme and user. Tailoring and personalization are achieved by adjusting content to expressed preferences and endorsed characteristics (e.g. current symptoms, desire for background detail or wish to skip optional sections).

Statistical analyses

Group differences in demographic data and pre-treatment measures were tested with independent-

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samples *t* tests and χ^2 tests where the variables consisted of nominal data. Differential outcomes at post-treatment were evaluated according to an intention-to-treat principle using a mixed-model repeated-measures analysis of variance with time (pre–post) as a within-group factor and treatment condition as a between-group factor. The mixed-effects models approach uses all available data of each subject and does not involve the substitution of missing values but estimates parameters about missing values (Gueorguieva & Krystal, 2004). We used an unstructured covariance structure for the analyses and estimated a separate model for each outcome measure. Significance testing of the diagnostic status at post-treatment was conducted with a χ^2 test. According to an intention-to-treat principle, dropouts were treated as treatment failures. Within- and between-group effect sizes (Cohen's *d*) were calculated based on estimated means and the pooled standard deviation from the observed means. Within-group changes in outcome scores from post-treatment to follow-up were analysed using paired *t* tests for completers.

Results

Baseline evaluation

The mean age of participants was 42.0 years (S.D. = 12.1, range = 18–72 years), and 98 were female (70.5% of the sample). The majority were married or in a relationship ($n = 86$, 61.9%) and were in full-time ($n = 49$, 35.3%) or part-time paid work ($n = 34$, 24.5%). Most of the participants had conducted an apprenticeship ($n = 57$, 41.0%) or indicated a university degree as their highest education ($n = 54$, 38.8%). In total, 57 participants (41.0%) were currently in psychotherapy and 47 (33.8%) were currently taking prescribed medication for anxiety or depression. A large percentage of the participants had attended psychotherapy in the past ($n = 108$, 77.7%). Most of the participants (129/139) initiated the participation in the study themselves (72/129 found the study website through search on the Internet, 48/129 read about the study in newspaper articles, and 8/129 received a recommendation by a friend). In 10 out of 139 cases, the MD informed the participants about the study. There were no between-group differences on demographic characteristics or other variables (see Table 2 for sample characteristics and between-group comparisons). Moreover, there were no pre-treatment differences between the groups on any of the primary and secondary outcome measures (p's > 0.18).

Diagnostic status according to the SCID

A total of 63 (45.3%) participants were diagnosed with PDA as their primary diagnosis, 40 (28.8%) met the criteria of a primary SAD diagnosis, and 36 (25.9%) participants were diagnosed with a primary GAD diagnosis. Axis I co-morbidity was high among participants: 45 (32.3%) suffered from a current major depressive episode (MDE), 42 (30.2%) from a co-morbid SAD, 26 (18.7%) from a co-morbid PDA, 22 (15.8%) from a co-morbid GAD, and 38 (27.3%) from a specific phobia. Moreover, 62 (44.6%) of the participants had suffered from an MDE in the past. Diagnostic status did not differ between groups at baseline (see Table 2).

Dropouts from the study and programme usage

Of the 139 individuals who were randomized, a total of 120 (86%) participants completed the post-treatment questionnaires (see Fig. 1). There were no significant differences in terms of demographics and pre-treatment scores between those who provided post-treatment data and those who did not (p's > 0.06). Mean time spent in the self-help programme was 13 h and 10 min (S.D. = 13 h 14 min; range = 0 min–83 h). The mean number of completed modules was 3.9 (S.D. = 2.3; range = 0–6 modules). In all, 32 participants (45.7%) completed all six modules. Eight (11.4%) participants did not start with the self-help programme. The mean number of CBM-I training sessions conducted between treatment modules was 4.4 (S.D. = 3.8; range = 0–17). Usage time and the number of completed modules correlated neither with pre-to-post changes nor with residual-gain scores of any of the outcome measures ($p > 0.08$).

Primary disorder-unspecific outcome measures and effect sizes in the overall sample at post-treatment

Observed and estimated means for all self-report measures are presented in Table 3. Linear mixed models with group as a fixed factor and time as a repeated factor (pre–post) were conducted separately for each of the dependent measures (see Table 3 for results). Main effects for the DASS-21, BAI, BDI-II, BSI and the mental health subscale of the SF-12 were qualified by significant group × time interactions [all F's (degrees of freedom 1, 118.7–125.0) > 11.8, all p's < 0.01]. Between-group effect sizes based on estimated means ranged between 0.41 (BAI) and 0.61 (BDI-II). Within-group comparisons based on estimated means in the treatment group revealed medium to large effect sizes (0.63–0.81). Within-group effect sizes in the control group clustered around zero (–0.07 to 0.22). No statistically significant group × time interaction was found on the physical health subscale of the SF-12 ($F_{1,122.6} = 1.74$, $p = 0.19$). In order to explore whether concurrent psychotherapy or taking prescribed medication during the treatment period moderated pre–post effects on the primary disorder-unspecific outcome measures, we included the respective variable

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Table 2. *Baseline demographics and sample characteristics for the treatment and control groups*

	Treatment group ($n = 70$)	Control group ($n = 69$)	Statistic
Mean age, years (standard deviation)	42.1 (12.2)	41.8 (12.2)	$t_{137} = 0.13$, $p = 0.90$
Gender, *n* (%)			$\chi^2_1 = 0.25$, $p = 0.62$
Male	22 (31)	19 (28)	
Female	48 (69)	50 (72)	
Marital status, *n* (%)			$\chi^2_3 = 0.99$, $p = 0.80$
Single/living alone	22 (31)	22 (32)	
Married/living together	43 (61)	43 (62)	
Divorced	4 (6)	4 (6)	
Widowed	1 (1)	0 (0)	
Highest education, *n* (%)			$\chi^2_3 = 1.68$, $p = 0.64$
Compulsory school	5 (7)	4 (6)	
Apprenticeship	32 (46)	25 (36)	
College	9 (13)	10 (14)	
University	24 (34)	30 (43)	
Employment, *n* (%)			$\chi^2_5 = 4.04$, $p = 0.54$
Full-time paid work	22 (31)	27 (39)	
Part-time paid work	21 (30)	13 (19)	
Unemployed	13 (19)	11 (16)	
At-home parent	2 (3)	3 (4)	
Student	2 (3)	5 (7)	
Retired	10 (14)	10 (15)	
Psychological treatment, *n* (%)			
Past	53 (76)	55 (80)	$\chi^2_1 = 0.32$, $p = 0.57$
Current	31 (44)	26 (38)	$\chi^2_1 = 0.63$, $p = 0.43$
Current medications, *n* (%)	26 (37)	21 (30)	$\chi^2_1 = 0.70$, $p = 0.40$
Primary diagnosis, *n* (%)			$\chi^2_2 = 0.24$, $p = 0.89$
Social anxiety disorder	19 (27)	21 (30)	
Panic disorder with/without agoraphobia	33 (47)	30 (44)	
Generalized anxiety disorder	18 (26)	18 (26)	
Co-morbid diagnoses, *n* (%)			
Current major depressive episode	20 (29)	17 (25)	$\chi^2_1 = 0.28$, $p = 0.60$
Past major depressive episode	29 (41)	33 (48)	$\chi^2_1 = 0.58$, $p = 0.49$
Dysthymia	12 (17)	17 (25)	$\chi^2_1 = 1.18$, $p = 0.28$
Social anxiety disorder	20 (29)	22 (32)	$\chi^2_1 = 0.18$, $p = 0.71$
Panic disorder with/without agoraphobia	15 (21)	11 (16)	$\chi^2_1 = 0.69$, $p = 0.41$
Generalized anxiety disorder	11 (16)	11 (16)	$\chi^2_1 = 0.01$, $p = 0.97$
Specific phobia	18 (26)	20 (29)	$\chi^2_1 = 0.19$, $p = 0.67$

in the mixed-models analyses and tested the significance of the three-way interaction between time, group and concurrent psychotherapy or medication. In these analyses, none of the three-way interactions attained significance (all p's > 0.06), indicating that neither concurrent psychotherapy nor using prescribed medication moderated the treatment effect on any of the primary outcome measures.

Secondary disorder-specific outcome measures and effect sizes in the overall sample at post-treatment

Based on the linear mixed models, all group × time interaction effects for the disorder-specific measures PSWQ, SPS, SIAS, ACQ and BSQ were significant [all F's (degrees of freedom 1, 118.3–125.5) > 0.61, all p's < 0.05] (see Table 2). Between-group effect sizes based on estimated means were small to medium, ranging from 0.17 (PSWQ) to 0.46 (SIAS). Within-group comparisons based on estimated means for the treatment group revealed medium effect sizes (0.52–0.59). Within-group effect sizes in the control group were small (0.07–0.14). Three-way interactions between time, group and concurrent psychotherapy or medication were not significant (all p's > 0.32). Thus, concurrent treatment did not appear to moderate the treatment effect on any of the secondary outcome measures.

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Disorder-specific outcome measures and effect sizes in the diagnostic subgroups at post-treatment

We also analysed group differences on disorder-specific measures separately for each anxiety diagnosis as assessed at pre-treatment. The three subgroups consisted of 82 participants with a SAD diagnosis, 89 participants with a PDA diagnosis, and 58 participants meeting the criteria of GAD as a primary or co-morbid disorder at pretreatment. Observed and estimated means for each group and all disorder-specific measures are presented in Table 4. Mixed-models analyses revealed either significant or marginally significant group × time interaction effects in each subgroup [all *F*s (degrees of freedom 1, 50.0–76.2) > 0.38, all *p*'s < 0.06] (see Table 4 for detailed results). In the SAD subgroup, between-group effect sizes based on estimated means were 0.53 on the SPS and 0.54 on the SIAS. In the PDA subgroup, between-group effect sizes ranged between 0.22 (MIB) and 0.45 (ACQ). In the GAD subgroup, between-group effect sizes were at 0.34 on the PSWQ and at 0.56 on the BDI-II.

Diagnostic response rates

In the analyses of the diagnostic response rates at post-treatment, dropouts from the SCID (i.e. 14/70 in the treatment group, and 9/69 in the control group) were regarded as non-responders. Among participants who fulfilled the diagnostic criteria for SAD at pre-treatment ($n = 82$), 11/39 (28.2%) of the participants in the treatment group and 2/43 (4.7%) in the control group no longer met diagnostic criteria for SAD ($\chi^2_1 = 8.5$, $p < 0.01$). Among participants who met the diagnostic criteria for PDA at pre-treatment ($n = 88$), 18/47 (38.3%) in the treatment group and 4/41 (9.8%) in the control group no longer fulfilled the criteria for PDA at post-treatment ($\chi^2_1 = 9.5$, $p < 0.01$). Among participants with a GAD diagnosis at pre-treatment ($n = 58$), 13/29 (44.8%) recovered in the treatment group, and 0/29 (0%) in the control group ($\chi^2_1 = 16.8$, $p < 0.001$).

Follow-up and treatment satisfaction

Observed means and standard deviations at 6 months after randomization (treatment group only) for all self-report measures are presented in Tables 3 and 4. Based on the completers sample, there were no significant post-treatment to follow-up changes for any of the primary and secondary outcome measures (*t*'s = 0.09–0.92, degrees of freedom = 40–41, *p*'s = 0.36–0.93), with one exception: The score on the BSQ further decreased significantly from post-treatment to follow-up ($t = 2.52$, degrees of freedom = 40, $p < 0.05$). Participants reported a high level of satisfaction with the self-help programme. The mean score on the CSQ-8 was 3.23 (S.D. = 0.51), lying between somewhat satisfied (3) and very satisfied (4).

Discussion

This study was the first investigation of the efficacy of a new transdiagnostic unguided ICBT intervention for three anxiety disorders, which was delivered after a contact with an MD in primary care. The findings indicate that this unguided ICBT – velibra – when delivered in this way is effective in reducing symptomatology and in increasing psychological well-being assessed as early as 9 weeks after treatment initiation. Between-group effect sizes after 9 weeks were in the small to medium range. In the treatment group, conservative estimates in which dropouts were regarded as treatment failures suggested that 28.2% of the participants with a SAD diagnosis, 38.3% of the participants with a PDA diagnosis, and 44.8% of the participants with a GAD diagnosis at pre-treatment no longer fulfilled diagnostic criteria at post-treatment, whereas such recovery was observed among fewer than 10% of participants in the CAU-only control condition. Furthermore, treatment gains were maintained up to 6 months after randomization. Given that (*a*) almost 80% of the participants had been treated with psychotherapy in the past, (*b*) 41% of participants were currently in psychotherapy, (*c*) approximately one-third of the participants were on stable medication for their condition, and (*d*) participants showed high co-morbidity rates, these results are encouraging.

In contrast to other studies conducted in primary care, participants were recruited not only through their primary care contact, but were also allowed to initiate participation in the study independently. In the latter case, they were required to undergo a face-to-face consultation with an MD prior to being permitted access to the study and the use of the self-help programme. This initial medical examination ensured diagnostic fit and improved client safety. In this study, 92.8% of all participants initiated participation in the study themselves and then consulted an MD, indicating that this delivery model of unguided ICBT is feasible and promising for the dissemination of unguided ICBT in primary care. Moreover, an examination of the participant flow through the trial shows that the number of participants lost prior to randomization and from pre- to post-treatment was lower than the numbers reported in a meta-analysis of computerized CBT treatments (Waller & Gilbody, 2009). This finding may be related to at least two aspects of the current trial. First, it is likely that the need for a consultation with an MD increased the threshold to participate, resulting in a selection of patients who

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Table 3. *Observed and estimated means for primary and secondary outcome measures and within- and between-group effect sizes*

	Pre-treatment		Post-treatment (observed)		Post-treatment (estimated)		Follow-up (observed)		Post-treatment between-group comparisons[a]	Pre–post within-group effect sizes (estimated means)	Between-group effect sizes at post-treatment (estimated means)
Measure	Mean (S.D.)	*n*	Mean (S.D.)	*n*	Mean (S.E.)	*n*	Mean (S.D.)	*n*	*F* and df	Cohen's *d* (95% CI)	Cohen's *d* (95% CI)
DASS-21											
Treatment	58.2 (24.4)	70	40.9 (25.7)	57	40.8 (3.09)	70	41.9 (30.0)	44	$F_{1,123.4} = 11.8$	0.69 (0.21–1.18)	0.47 (0.13–0.81)
Control	55.8 (21.3)	69	52.7 (24.7)	63	52.6 (3.00)	69			$p < 0.01$	0.14 (−0.61 to 0.33)	
BAI											
Treatment	34.9 (9.1)	70	27.8 (9.1)	57	27.5 (1.22)	70	26.6 (9.4)	44	$F_{1,125.0} = 12.9$	0.81 (0.33–1.30)	0.41 (0.07–0.74)
Control	33.3 (10.3)	69	31.4 (10.0)	63	31.5 (1.19	69			$p < 0.001$	0.18 (−0.65 to 0.30)	
BDI-II											
Treatment	22.6 (10.6)	70	15.8 (12.4)	57	15.3 (1.54)	70	16.3 (13.7)	44	$F_{1,118.7} = 34.9$	0.63 (0.15–1.11)	0.61 (0.27–0.95)
Control	22.0 (11.0)	69	22.9 (12.6)	63	22.9 (1.52)	69			$p < 0.001$	−0.07 (−0.40 to 0.54)	
BSI											
Treatment	1.34 (0.56)	70	0.94 (0.63)	57	0.90 (0.09)	70	0.97 (0.77)	44	$F_{1,118.7} = 14.9$	0.74 (0.25–1.22)	0.42 (0.08–0.75)
Control	1.27 (0.57)	69	1.18 (0.71)	63	1.18 (0.08)	69			$p < 0.001$	0.22 (−0.69 to 0.25)	
SF-12 MH											
Treatment	31.2 (8.8)	70	37.5 (11.8)	57	37.9 (1.30)	70	39.9 (12.2)	44	$F_{1,119.2} = 33.1$	0.64 (0.16–1.12)	0.49 (0.15–0.83)
Control	33.2 (9.5)	69	33.0 (9.2)	63	32.7 (1.27)	69			$p < 0.001$	−0.05 (−0.53 to 0.44)	
SF-12 PH											
Treatment	48.5 (11.2)	70	48.3 (11.4)	57	48.7 (1.29)	70	48.6 (11.1)	44	$F_{1,122.6} = 1.74$	−0.02 (−0.49 to 0.45)	0.16 (−0.17 to 0.50)
Control	48.3 (10.8)	69	47.2 (9.5)	63	47.0 (1.27)	69			$p = 0.19$	−0.11 (−0.58 to 0.36)	
PSWQ											
Treatment	62.7 (9.3)	70	58.4 (11.1)	57	57.4 (1.62)	70	58.0 (10.9)	44	$F_{1,118.3} = 6.1$	0.52 (0.04–1.00)	0.17 (−0.16 to 0.50)
Control	60.4 (11.0)	69	60.0 (13.5)	63	59.5 (1.57)	69			$p < 0.05$	0.07 (−0.40 to 0.54)	
SPS											
Treatment	29.1 (17.2)	70	20.9 (13.4)	57	20.9 (1.97)	70	20.0 (16.2)	44	$F_{1,123.5} = 13.2$	0.53 (0.06–1.01)	0.38 (0.05–0.72)
Control	28.7 (17.5)	69	27.1 (18.0)	63	27.0 (1.94)	69			$p < 0.001$	0.10 (−0.38 to 0.57)	
SIAS											
Treatment	37.5 (17.3)	70	28.2 (15.0)	57	28.5 (1.98)	70	29.1 (15.2)	44	$F_{1,122.4} = 27.9$	0.56 (0.08–1.09)	0.46 (0.12–0.80)
Control	37.0 (16.2)	69	36.0 (17.5)	63	36.0 (1.97)	69			$p < 0.001$	0.06 (−0.41 to 0.53)	
ACQ											
Treatment	2.13 (0.62)	70	1.81 (0.64)	57	1.76 (0.07)	70	1.69 (0.57)	44	$F_{1,121.7} = 26.3$	0.59 (0.14–1.10)	0.35 (0.02–0.69)
Control	2.06 (0.61)	69	1.97 (0.61)	63	1.98 (0.08)	69			$p < 0.001$	0.13 (−0.34 to 0.60)	

Table 3 (*cont.*)

Measure	Pre-treatment		Post-treatment (observed)		Post-treatment (estimated)		Follow-up (observed)		Post-treatment between-group comparisons[a]	Pre–post within-group effect sizes (estimated means)	Between-group effect sizes at post-treatment (estimated means)
	Mean (S.D.)	*n*	Mean (S.D.)	*n*	Mean (S.E.)	*n*	Mean (S.D.)	*n*	*F* and df	Cohen's *d* (95% CI)	Cohen's *d* (95% CI)
BSQ											
Treatment	2.64 (0.86)	70	2.23 (0.77)	57	2.20 (0.10)	70	2.01 (0.86)	44	$F_{1,122.9} = 9.8$	0.54 (0.06–1.01)	0.24 (−0.09 to 0.58)
Control	2.47 (0.78)	69	2.36 (0.80)	63	2.39 (0.10)	69			$p < 0.01$	0.14 (−0.33 to 0.61)	

S.D., Standard deviation; S.E., standard error; df, degrees of freedom; CI, confidence interval; DASS-21, Depression Anxiety Stress Scales; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory – second edition; BSI, Brief Symptom Inventory; SF-12 MH, Short Form Health Survey mental health subscale; SF-12 PH, Short Form Health Survey physical health subscale; PSWQ, Penn State Worry Questionnaire; SPS, Social Phobia Scale; SIAS, Social Interaction Anxiety Scale; ACQ, Agoraphobic Cognitions Questionnaire; BSQ, Body Sensations Questionnaire.

[a] Intention-to-treat analysis.

were strongly motivated to participate in the study. Second, as mentioned in the Introduction, the transdiagnostic nature of the treatment addressed a relatively broad range of patients, resulting in fewer individuals who needed to be excluded from the study because they did not fulfill the criteria of only one specific diagnosis. The relatively few exclusions and dropouts speak for the external validity of this study. The results may thus generally apply to a population that is willing to consult an MD because of anxiety symptoms and that is motivated to use an Internet-based self-help programme.

This study has several limitations. First, although participants in the control group could receive any treatment they actively sought, they did not receive an active treatment as part of the study. Because participants could therefore not be blinded to treatment allocation, we cannot infer the extent to which the observed effects are uniquely caused by the specific intervention under study. At the same time, our findings provide evidence for the efficacy of only this particular intervention and cannot be generalized to other programmes. A second limitation concerns the limited power of this study, which did not permit us to detect small differences in each of the diagnostic subgroups. Given resource limitations, recruitment was terminated after 139 randomized patients rather than the original aim of 176 patients. With this sample size, we still had sufficient power (>0.80) to detect medium effects between the intervention and control group, but insufficient power to detect small effects. A third limitation is related to the fact that the sample was better educated than the general population. This common observation in studies on Internet-based treatments limits the generalizability of our results and raises the question whether less educated individuals would also benefit from the intervention. A fourth limitation is that we do not have information about the exact amount, dose and quality of concurrent CAU for the treatment and control groups. Further limitations were that the inter-rater agreement of the clinical interviewers was not assessed, and that interviewers could not be kept blind regarding group assignment at post-assessment. Finally, the dropout rate at follow-up was relatively high, although it was low at post-treatment. The absence of a comparison group at follow-up does not allow us to infer the extent to which observed maintenance effects can be attributed to the intervention.

Despite these limitations, the current study provides evidence that this transdiagnostic unguided ICBT programme (velibra) for three common anxiety disorders is effective when delivered in primary care. Future research efforts are needed to compare this intervention with other active treatments, to better understand for

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Table 4. *Observed and estimated means for disorder-specific outcome measures for each diagnostic group and within- and between-group effect sizes*

	Pre-treatment		Post-treatment (observed)		Post-treatment (estimated)		Follow-up (observed)		Post-treatment between-group comparisons[a]	Pre–post within-group effect sizes (estimated means)	Between-group effect sizes at post (estimated means)
Measure	Mean (S.D.)	*n*	Mean (S.D.)	*n*	Mean (S.E.)	*n*	Mean (S.D.)	*n*	*F* and df	Cohen's *d* (95% CI)	Cohen's *d* (95% CI)
Participants with a SAD diagnosis											
SPS											
Treatment	36.7 (16.7)	39	26.2 (15.1)	30	25.7 (2.68)	39	27.0 (18.4)	23	$F_{1,70.1} = 15.5$	0.69 (0.05–1.34)	0.53 (0.09–0.97)
Control	35.9 (15.5)	43	34.2 (16.7)	40	34.2 (2.46)	43			$p < 0.001$	0.11 (−0.49 to 0.70)	
SIAS											
Treatment	47.4 (14.5)	39	35.6 (14.5)	30	35.6 (2.47)	39	37.6 (14.3)	23	$F_{1,70.0} = 27.3$	0.81 (0.16–1.47)	0.54 (0.10–0.98)
Control	45.0 (14.9)	43	43.6 (15.6)	40	43.7 (2.28)	43			$p < 0.001$	0.09 (−0.51 to 0.68)	
Participants with a PDA diagnosis											
ACQ											
Treatment	2.24 (0.64)	48	1.94 (0.68)	40	1.88 (0.10)	48	1.79 (0.60)	30	$F_{1,76.2} = 3.9$	0.55 (−0.03 to 1.12)	0.45 (0.03–0.87)
Control	2.29 (0.58)	41	2.05 (0.66)	36	2.18 (0.11)	41			$p = 0.05$	0.18 (−0.44 to 0.80)	
BSQ											
Treatment	2.86 (0.67)	48	2.43 (0.74)	40	2.40 (0.11)	48	2.22 (0.85)	30	$F_{1,74.7} = 4.6$	0.65 (0.07–1.23)	0.41 (−0.01 to 0.83)
Control	2.83 (0.54)	41	2.68 (0.72)	36	2.70 (0.12)	41			$p < 0.05$	0.20 (−0.42 to 0.83)	
MIA											
Treatment	2.69 (1.04)	48	2.40 (1.08)	40	2.42 (0.15)	48	2.17 (1.06)	30	$F_{1,74.3} = 5.2$	0.26 (−0.31 to 0.82)	0.34 (−0.08 to 0.76)
Control	2.84 (0.89)	41	2.74 (0.92)	36	2.76 (0.16)	41			$p < 0.05$	0.09 (−0.53 to 0.71)	
MIB											
Treatment	2.12 (0.98)	48	1.84 (0.88)	40	1.87 (0.13)	48	1.74 (0.93)	30	$F_{1,74.3} = 10.9$	0.27 (0.03–0.84)	0.22 (−0.20 to 0.64)
Control	2.09 (0.75)	41	2.07 (0.82)	36	2.06 (0.14)	41			$p < 0.01$	0.04 (−0.58 to 0.66)	
Participants with a GAD diagnosis											
PSWQ											
Treatment	67.6 (7.0)	29	63.0 (11.2)	26	62.8 (1.97)	29	61.7 (10.4)	22	$F_{1,50.3} = 3.8$	0.51 (−0.23 to 1.25)	0.34 (−0.17 to 0.86)
Control	66.7 (9.2)	29	66.3 (9.1)	26	66.3 (1.97)	29			$p = 0.06$	0.04 (−0.68 to 0.77)	
BDI-II											
Treatment	27.0 (10.3)	29	19.1 (13.6)	26	18.7 (2.5)	29	18.6 (15.8)	22	$F_{1,50.0} = 19.4$	0.69 (−0.06–1.44)	0.56 (0.04–1.09)
Control	24.4 (10.0)	29	25.4 (12.8)	26	26.1 (2.5)	29			$p < 0.001$	−0.15 (−0.88 to 0.58)	

S.D., Standard deviation; S.E., standard error; df, degrees of freedom; CI, confidence interval; SAD, social anxiety disorder; SPS, Social Phobia Scale; SIAS, Social Interaction Anxiety Scale; PDA, panic disorder with/without agoraphobia; ACQ, Agoraphobic Cognitions Questionnaire; BSQ, Body Sensations Questionnaire; MIA, Mobility Inventory for Agoraphobia, Avoidance Alone; MIB, Mobility Inventory for Agoraphobia, Avoidance Accompanied; GAD, generalized anxiety disorder; PSWQ, Penn State Worry Questionnaire; BDI-II, Beck Depression Inventory – second edition.

[a] Intention-to-treat analysis.

whom and how it is effective, to determine its cost-effectiveness, and to investigate how it could be implemented on a larger scale so that it can contribute to alleviating the global burden associated with these anxiety disorders.

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Declaration of Interest

The last author (B.M.) is employed as research director at Gaia AG, the company that developed, owns and operates the Internet intervention investigated in this trial. All the other authors report no relationships with commercial interests.

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