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Review article

The effectiveness and cost-effectiveness of e-health interventions for depression and anxiety in primary care: A systematic review and meta-analysis[☆]

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ABSTRACT

Purpose: Psychological interventions are labor-intensive and expensive, but e-health interventions may support them in primary care. In this study, we systematically reviewed the effectiveness and cost-effectiveness of e-health interventions for depressive and anxiety symptoms and disorders in primary care.

Methods: We searched MEDLINE, Cochrane library, Embase, and PsychINFO until January 2018, for randomized controlled trials of e-health interventions for depression or anxiety in primary care. Two reviewers independently screened the identified publications, extracted data, and assessed risk of bias using the Cochrane Collaboration's tool.

Results: Out of 3617 publications, we included 14 that compared 33 treatments in 4183 participants. Overall, the methodological quality was poor to fair. The pooled effect size of e-health interventions was small (standardized mean difference = −0.19, 95%CI −0.31 to −0.06) for depression compared to control groups in the short-term, but this was maintained in the long-term (standardized mean difference = −0.22, 95%CI −0.35 to −0.09). Further analysis showed that e-health for depression had a small effect compared to care as usual and a moderate effect compared to waiting lists. One trial on anxiety showed no significant results. Four trials reported on cost-effectiveness.

Limitations: The trials studied different types of e-health interventions and had several risks of bias. Moreover, only one study was included for anxiety.

Conclusions: E-health interventions for depression have a small effect in primary care, with a moderate effect compared to waiting lists. The approach also appeared to be cost-effective for depression. However, we found no evidence for its effectiveness for anxiety.

1. Background

Depressive and anxiety disorders are common in the general population, with around 20% of adults suffering from either disorder at some time during their lives (de Graaf et al., 2012). The disorders are associated with high burden of disease and vast societal costs (Whiteford et al., 2013; Smit et al., 2006). Most patients with a

depressive or anxiety disorder (>80%) are treated in general practice (Kessler et al., 2003; Verhaak et al., 2009), where around three-quarters will receive pharmacotherapy (Wilson et al., 2003). However, in the milder cases seen in primary care, this approach has questionable effectiveness (Fournier et al., 2010) and is associated with side effects (Ferguson, 2001; Sanchez et al., 2015), poor adherence (Simon et al., 2001; Lewis Elizabeth, 2004), and addiction or discontinuation

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problems (Guina and Merrill, 2018). Perhaps unsurprisingly, most patients therefore prefer psychological treatment (van Schaik et al., 2004), typically requiring prolonged attention and counseling in primary care (Backenstrass et al., 2007; Sibbald et al., 1993). By contrast, structured psychotherapy such as cognitive behavioral therapy (CBT) is rarely offered (Weisberg et al., 2014). For this reason, general practitioners (GPs) have expressed the need for effective psychological treatments that can be used in primary care, though a lack of time and experience often means that they fail to be provided (Telford et al., 2002; Mykletun et al., 2010; Nutting et al., 2002).

The importance of facilitating GPs in delivering mental health care is widely recognized, and one proposed solution has been to offer e-health interventions to support psychological treatments in primary care. By offering guided support or self-help services online, it is thought that access to psychological treatment, and the time and costs involved in its delivery, can be improved (i.e. therapist and transportation costs) (Eells et al., 2014). Systematic reviews and meta-analyses indicate that guided e-health interventions may be particularly effective for patients with depressive or anxiety disorders, even being comparable to face-to-face interventions (Andersson et al., 2014; Andrews et al., 2010). However, these meta-analyses have combined the results from studies with mixed populations, including general, primary care, and specialist care populations. This is important because the primary care population differs from the others, notably in terms of help-seeking behavior and acceptance of treatment. For example, patients mostly self-refer in the general population, unlike in primary and secondary care. Even in primary care, patients are often less accepting of treatment than in specialist care due to a lower perceived need and more negative attitudes toward antidepressant medication or counseling (Van Voorhees et al., 2003).

In primary care, there is considerable heterogeneity in the severity of mental health problems (Watts, 1984), with a higher prevalence of patients with mild–moderate symptoms compared with specialist care (Coyne et al., 1994; Katon and Schulberg, 1992). The psychological treatments on which e-health interventions are based are also reported to be most effective for patients with symptoms that are more severe (Driessen et al., 2010). Within-study severity analyses have shown that post-treatment effect sizes are higher for patients with severe disease than for those with mild disease (Cuijpers et al., 2009). Thus, it has been concluded that psychological treatment may be less effective in primary care than in other settings (community self-referrals or specialist mental health care), at least in part, because of the lower motivation associated with the less disabling symptoms among patients in primary care (Cuijpers et al., 2009). Given that treatment preference influences the outcome of interventions, clinical effectiveness reduces commensurately (Dunlop et al., 2012; Magnani et al., 2016). Overall, therefore, differences between populations may have affected the generalizability of the previous studies and meta-analyses.

We systematically reviewed the effectiveness and cost-effectiveness of e-health interventions for depressive and anxiety symptoms and disorders among patients recruited and treated in primary care.

2. Materials and methods

2.1. Reporting

In this report, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline (Appendix 1) (Liberati et al., 2009). The systematic review protocol was also registered at Prospero (CRD42016037452).

2.2. Study inclusion criteria

We included original reports that met the following criteria: (A) randomized controlled trials (RCTs) with primary data; (B) comparing guided or self-guided e-health interventions to active controls but not e-health, waitlist controls, or no intervention.; (C) including adult

patients (≥ 18 years old) with depressive and/or anxiety symptoms or with a primary diagnosis of a depressive and/or anxiety disorder, excluding obsessive compulsive disorder or posttraumatic stress disorder; (D) performed in primary care; and (E) considering the effectiveness of an e-health intervention in reducing depressive and anxiety symptoms, as measured by a validated observer and/or self-report measure. For inclusion in the meta-analysis, a study needed to report a mean difference, a risk or odds ratio for response or remission, or to provide the information needed to calculate these. If this information was not available in the report, we first contacted the corresponding authors, and only excluded the study if the data were not available.

Key to this research was the definition of what constituted an e-health intervention, particularly guided and self-guided interventions. We defined guided interventions as those in which participants were pro-actively supported by a person during treatment (e.g., providing motivation, answering questions, or tackling uncertainties). Self-guided interventions were defined as all other interventions where personal support was not offered during treatment; solely technical support was also considered self-guided. Otherwise, e-health interventions were defined according to the definition of e-mental health by Riper et al. (2010) as “a generic term to describe the use of information and communication technology (ICT)—in particular the many technologies related to the Internet—when these technologies are used to support and improve mental health conditions and mental health care, including care for people with substance use and comorbid disorders [sic].” Examples of eligible e-health interventions for this review were web-based interventions, mobile apps, e-mail therapy, chat therapy, and video therapy. We focused on interventions offered in primary care by a primary care caregiver, such as a general practitioner, nurse practitioner, or psychotherapist. Specialist care was considered that provided within psychiatry, such as outpatient and inpatient clinics, including ambulatory care.

2.3. Study exclusion criteria

We excluded studies in which participants with psychosis, bipolar disorder, or cognitive impairment were included. We also excluded studies with self-referred patients, recruited through community advertisements and websites, because we considered these to constitute a community population rather than a primary care population.

2.4. Search methods for identifying studies

To provide an updated review, the first author performed a search of electronic databases (MEDLINE, Cochrane library, Embase, and PsychINFO) to January 2018, using the following search terms: “E-health intervention” AND (depressive disorder OR depressive symptoms OR anxiety disorder OR anxiety symptoms) AND “primary care.” We applied the highly sensitive Cochrane filter for RCTs (Lefebvre et al., 2011), used several synonyms for the search terms (Appendix 2). We set no language or date restrictions. Duplicate files were identified and removed. Clinical trials registries (clinicaltrials.gov and <http://www.who.int/trialsearch>) were searched for unpublished trials. Finally, the reference sections of identified trials and relevant systematic reviews were checked for additional trials.

2.5. Selection and quality assessment of eligible studies

First, two reviewers (BM and FH) independently screened titles and abstracts to identify eligible studies. Second, full texts were reviewed to check the identified studies against the inclusion and exclusion criteria. A third reviewer (MHB) independently decided on the inclusion of studies for which no consensus was reached. Third, two reviewers (BM and FH) independently assessed the risk of bias and the methodological quality of the included papers based on the Cochrane Collaboration tool (Higgins et al., 2011). Disagreement was resolved by consensus, or by the consultation of a third reviewer (MHB).

2.6. Data extraction

A predefined form was used to extract information about study design, trial characteristics (country, publication year), participant characteristics, e-health intervention characteristics, follow-up duration, handling of loss to follow-up, short-term and long-term outcomes, and extent of withdrawals. The characteristics extracted for the e-health interventions were: (de Graaf et al., 2012) whether guided or self-guided, (Whiteford et al., 2013) the content of the intervention, and (Smit et al., 2006) the mode of therapy. Each included study was carefully crosschecked to ensure that no overlapping data were present.

2.7. Data synthesis

We first assessed the heterogeneity of the included studies and then calculated the short- and long-term effects of the e-health interventions for depression and anxiety. Short-term effects were based on follow-up to four months and long-term effects were based on follow-up beyond six months. For the effect size calculations, we used outcome instruments that explicitly measured depression or anxiety symptoms, and then used the standardized mean difference (SMD) to calculate the pooled effect size in the meta-analysis. If not reported, we calculated the SMD as Hedges' *g*. Effect sizes of 0.8, 0.5, and 0.2 were considered large, moderate, and small, respectively (Cohen, 1988). If more than one outcome measure was reported, only the primary outcome was used. If the primary outcome was not stated, we calculated the mean of the effect sizes for all outcome measurements.

Before analysis, we anticipated that substantial heterogeneity would exist between studies, so we used a random-effects model to summarize the outcomes. We pooled data if three or more studies were available, using the random-effects model in RevMan (DerSimonian and Laird, 1986). Three analyses were performed to compare guided or self-guided e-health interventions as the index group with one of three control groups (de Graaf et al., 2012) any active control but no e-health, (Whiteford et al., 2013) care as usual, and (Smit et al., 2006) waiting list or no intervention). Further, we compared the risk of bias (i.e. low, unclear, and high) across the studies in a subgroup analysis, which was decided during the review process, deviating from the study protocol. We tested for publication bias by inspecting the funnel plots on short-term outcome measures of depressive symptoms.

3. Results

3.1. Trial selection

The primary search identified 4556 citations, of which 3617 were unique. Reference checking of relevant systematic reviews (Eells et al., 2014; Eysenbach et al., 2004; Olthuis et al., 2016; Andrews and Williams, 2015; Aboujaoude et al., 2015; Spek et al., 2007) and of the included studies identified an additional 28 citations. We then excluded 3522 studies based on review of the titles and abstracts, and another 104 after full text review (Fig. 1). Finally, we included 14 relevant RCTs comparing 33 treatments in 4183 participants (Hallgren et al., 2016; Kivi et al., 2014; Hoifodt et al., 2013; Levesque et al., 2011; Moreno et al., 2012; Montero-Marin et al., 2016; Nordgren et al., 2014; Simon et al., 2011; Silverstone et al., 2017; Salisbury et al., 2016; Gilbody et al., 2015; Hilty et al., 2007; Kessler et al., 2009; Burton et al., 2016).

3.2. Description of the trials

Thirteen trials were of patients with depressive symptoms or disorders (Hallgren et al., 2016; Kivi et al., 2014; Hoifodt et al., 2013; Levesque et al., 2011; Moreno et al., 2012; Montero-Marin et al., 2016; Simon et al., 2011; Silverstone et al., 2017; Salisbury et al., 2016; Gilbody et al., 2015; Hilty et al., 2007; Kessler et al., 2009; Burton et al., 2016), but only one was of patients with anxiety disorders

(Nordgren et al., 2014). Twelve trials were performed to study guided e-health interventions, but these had varying levels of guidance (i.e., number and duration of sessions) delivered by different professionals (i.e. administrative worker, physician, or therapist). One trial was performed to compare guided and self-guided e-health interventions to care as usual (Montero-Marin et al., 2016), and another trial studied a self-guided e-health intervention (Levesque et al., 2011). However, the level and type of guidance was unclear in another trial (Silverstone et al., 2017). The publication dates ranged between 2007 and 2017, and four studies reported on cost-effectiveness (Nordgren et al., 2014; Hollinghurst et al., 2010; Romero-Sanchiz et al., 2017; Littlewood et al., 2015). The duration of follow-up varied between 4 weeks and 24 months and the sample size ranged from 28 to 946. A description and summary of each trial is shown in Table 1.

3.3. Risk of bias

The quality of the 14 studies ranged from poor to fair, with each study having methodological limitations (Fig. 2). Overall, there was a low risk of bias for 46.7% of the items, an unclear risk for 23.8%, and a high risk for 29.5%. We found no evidence of publication bias, with analysis showing a symmetric funnel plot (Fig. 3).

3.4. Outcomes

3.4.1. Depressive symptoms and disorders

We pooled the data on post-treatment depressive symptoms from 12 trials (Table 2) (Hallgren et al., 2016; Kivi et al., 2014; Hoifodt et al., 2013; Levesque et al., 2011; Moreno et al., 2012; Montero-Marin et al., 2016; Simon et al., 2011; Silverstone et al., 2017; Salisbury et al., 2016; Gilbody et al., 2015; Kessler et al., 2009; Burton et al., 2016; Hallgren et al., 2015; Eriksson et al., 2017), though one trial was excluded from the meta-analysis because of incomplete and inaccurately reported effect sizes (Hilty et al., 2007). Both short-term (11 trials, 3321 participants, Fig. 4) and long-term outcomes (9 trials, 3,042 participants, Fig. 5) were reported. Compared to all control groups combined, e-health interventions showed small but statistically significant pooled effects in the short-term (SMD = −0.19, 95% CI −0.31 to −0.06) and long-term (SMD = −0.22, 95% CI −0.35 to −0.09). Compared to care as usual, most trials reported a positive effect (negative SMD), except for two studies that reported a negative effect for the e-health intervention (Kivi et al., 2014; Gilbody et al., 2015; Eriksson et al., 2017). The e-health interventions showed a small positive effect compared to care as usual, (SMD = −0.14, 95% CI −0.26 to −0.02) (Fig. 6), but compared to waiting lists or no treatment, they showed a moderate positive effect (SMD = −0.45, 95% CI −0.62 to −0.29) (Fig. 7). Subgroup analysis by overall risk of bias showed no significant differences (Appendix 3).

3.4.2. Anxiety symptoms and disorders

Only one trial was included that studied the treatment of anxiety disorders, and this was in a Swedish primary care setting (Table 2) (Nordgren et al., 2014). In this trial, the authors compared text-based CBT guided by a clinical psychologist through e-mail against two control conditions, i.e. usual primary care access and being placed on a waiting list. Unfortunately, this study only showed a non-significant effect size at 10 weeks (Cohen's *d* = 0.58, *p* = 0.68).

3.4.3. Cost-effectiveness

Four trials reported data on the cost-effectiveness of internet-delivered CBT (Appendix 4). Littlewood et al. (2015) showed that usual primary care provision for depression was probably more cost-effective at a £20,000 per quality-adjusted life year (QALY) threshold than either of two guided e-health interventions alongside usual primary care in most scenarios, with probabilities ranging from 0.545 to 0.619. Indeed, there were no major differences in clinical effectiveness or cost-

* Exclusion of one RCT (two articles) comparing guided vs. self-guided e-health without inclusion of a non-e-health control group.

Fig. 1. Flow diagram of the systematic search and review process.

* Exclusion of one RCT (two articles) comparing guided vs. self-guided e-health without inclusion of a non-e-health control group.

effectiveness outcomes between the groups. [Hollingshurst et al. \(2010\)](#) found that a guided e-health intervention for depression was 94% likely to be cost-effective at a willingness to pay £20,000 per QALY when compared to waiting lists. However, [Romero-Sanchiz et al. \(2017\)](#) showed that both guided and self-guided e-health interventions for depression were more cost-effective than care as usual, with incremental cost-effectiveness ratios (ICERs) of -€9.91 and -€98.37 and savings of €496.72 and €5140.40, respectively, per QALY gain. [Nordgren et al. \(2014\)](#) reported that guided e-health interventions for anxiety were probably cost-effective, with an ICER of -\$1824 (-\$616/0.34) after treatment in favor of guided e-health over care as usual. For each incremental improvement in the outcome measure, internet-delivered CBT by guided e-health generated a societal earning of \$1824 relative to the control condition; each additional QALY therefore generated \$7523 compared with care as usual ([Nordgren et al., 2014](#)).

4. Discussion

4.1. Summary of main findings

In this systematic review and meta-analysis, we summarized the effectiveness of e-health interventions in 14 RCTs that included 4183

patients with depressive or anxiety symptoms or disorders in primary care settings. Cost-effectiveness was reviewed in four studies.

The meta-analysis showed a small effect size for e-health interventions delivered in primary care to treat depressive symptoms and disorders. Among these patients, there was a small positive and statistically significant short-term effect compared to all control groups combined, and this was maintained in the long term. However, the effects varied somewhat between studies, with most showing non-significant positive effects. Further analysis also showed that e-health interventions for depressive symptoms and disorders had a small effect size compared to care as usual and a moderate effect size compared to being placed on a waiting list for the study treatment or no treatment at all.

We found initial evidence regarding cost-effectiveness of e-health interventions in primary care settings. In three out of four studies, e-health interventions were more likely to be cost-effective compared to both care as usual ([Nordgren et al., 2014](#); [Romero-Sanchiz et al., 2017](#)) and to being placed on a waiting list ([Hollingshurst et al., 2010](#)). By contrast, a pragmatic RCT showed that the addition of an e-health intervention to usual treatment in primary care was no more cost-effective than care as usual (in CAU around 20% were offered e-health) ([Littlewood et al., 2015](#)).

Finally, we found limited evidence for the effectiveness and cost-effectiveness of e-health interventions for anxiety because there was a

Table 1
Characteristics of the included studies

#	First author (year)	Country	Diagnostic inclusion criterion	Baseline disease severity	Intervention	Content intervention	Mode of therapy	N ^a	Control	N ^b	Mean age (SD)	Ratio M:F	Use of antidepressant medication	Main outcome	Monitoring
Depressive disorder															
1	Burton et al. (2016)	Romania Spain and Scotland	MDD; diagnosis by treating clinician and BDI between 10–30	Mean BDI-II = 21 Mean QIDS-SR16 = 17 Mild = 52% Moderate = 22% Severe = 26%	Guided e-health intervention	Monitoring, psychoeducation, cognitive challenging, activation & relaxation	Web-based, individual therapy, guided by clinician, face-to-face at 2 and 4 weeks.	14	CAU	14	38 (nr)	9:18	Baseline: 38% ^a vs. 57% ^b	Not stated ^{**}	Monitoring with daily mood check
2	Gilbody et al. (2015) and (Littlewood et al. (2015)	United Kingdom	New or existing depression; assessed by CIS-R and PHQ-9 ≥ 10	Mean PHQ-9 = 17	Guided e-health intervention + CAU	Cognitive behavioural therapy	BTB ^c Web-based, individual therapy, guided by trained advisor, weekly telephonic, 1 intro of 15 min + 8 sessions of 50 min MoodGYM ^d Web-based, individual therapy, guided by trained advisor, weekly telephonic, 7 sessions	210 ^c 242 ^d	CAU	239	40 (nr)	229:462	During 1-year follow-up: 82% ^c vs. 84% ^b	PHQ-9 at 4 months	Not reported
3	Hallgren et al. (2015, 2016)	Sweden	Mild to moderate depression (PHQ-9 > 9)	Mean MADRS = 22	Guided e-health intervention	Cognitive behavioural therapy	Web-based, individual therapy, (on-demand) guided by psychologist, telephonic and text messages. Target: 13 sessions	317	Physical exercise ^e	317 ^e	Not reported	257:689	During 12-week intervention: 31% ^a vs. 31% ^e	MADRS	Weekly monitoring
4	Hilty et al. (2007)	USA	Major depression (as confirmed by SCID-I)	Mean BDI-13 = 18	Guided e-health intervention	Intensive disease management modules: includes psychoeducation, and video therapy with psychiatrist	Web-based, individual therapy, guided by PCP, nurse and psychiatrist, with visits, telephone calls and tele-psychiatric consultations respectively, 12 sessions.	52	CAU + disease management	41	46	19:75	During 12-week intervention: 31% ^a vs. 24% ^b	BDI-13	Unclear

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Table 1 (continued)

#	First author (year)	Country	Diagnostic inclusion criterion	Baseline disease severity	Intervention	Content intervention	Mode of therapy	N ^a	Control	N ^b	Mean age (SD)	Ratio M:F	Use of antidepressant medication	Main outcome	Monitoring
5	Kessler et al. (2009) and Hollinghurst et al. (2010)	England	New episode of depression: ICD-10 diagnosis according revised CIS and BDI ≥ 14	Mean BDI = 33 Mild = 5% Moderate = 27% Severe = 69%	Guided e-health intervention + CAU	Cognitive behavioural therapy	Chat-therapy, individual therapy, guided by psychologist, up to 10 sessions of 55 min	149	Waiting list, treatment after 8 months	148	34.9 (11.6)	95:202	54% ^a vs. 49% ^b	BDI: recovery (score ≤ 10) at 4 months	None
6	Kivi et al. (2014)/ Eriksson et al. (2017)	Sweden	Mild to moderate depression, as diagnosed by MINI and with MADRS < 35 longer than 2 weeks	Mean MADRS = 26 Minimal = 6% Mild = 19% Moderate = 34% Severe = 41%	Guided e-health intervention	Behavioural activation, Mindfulness and Acceptance and commitment therapy	Web-based intervention, individual therapy, guided by psychologist, telephonic and e-mail, 7 sessions within 8-12 weeks	45	CAU	47	36.6 (11.3)	27:52	Baseline: 24% a vs. 23% Post-treatment: 18% a vs. 38%	BDI-II	E-mail monitoring with MADRS at week 3 and 7
7	Levesque et al. (2011)	USA	Depression not involved in treatment and not planning to seek treatment in the next 30 days + PHQ-9 ≥ 5 and BDI ≥ 14	Mean BDI = nr Mild = 44% Moderate = 39% Severe = 17%	Self-guided e-health intervention	Trans theoretical model of behaviour change	Bibliotherapy + e-mails with computer-generated individualized feedback	174	No treatment	176	18-88	117:233		BDI-II	Monitoring of severity of depression and suicide risk
8	Montero-Marín et al. (2016) and Romero-Sánchez (2017)	Spain	Major depression with mild to moderate severity: BDI ≥ 14 and lasting longer than 2 weeks	Mean BDI = 22	Guided e-health intervention	Cognitive behavioural therapy and positive psychology	Web-based intervention, individual therapy, technical support and guided by psychologist through e-mail (maximum 3 contacts), 10 sessions	96	Self-guided e-health intervention	98	43 (10.3)	72:224		BDI-II	Self-monitoring activity report
9	Moreno et al. (2012)	USA	Major depressive episode; diagnosis by MINI and PHQ-9 ≥ 10	Mean PHQ-9 = 18 Mean MADRS = 29	Guided e-health intervention	Psychiatric intervention; including psychoeducation and medication management using measurement-based treatment	Videotherapy, individual therapy, guided by psychiatrist, 6 sessions of 20 min	80	CAU CAU	102 87	43.2 (11.9)	75:12	Not reported	Not stated***	Monitoring according to 'Texas medication algorithm project'

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Table 1 (continued)

#	First author (year)	Country	Diagnostic inclusion criterion	Baseline disease severity	Intervention	Content intervention	Mode of therapy	N ^a	Control	N ^b	Mean age (SD)	Ratio M:F	Use of antidepressant medication	Main outcome	Monitoring
10	Salisbury et al. (2016)	England	Depression, confirmed with CIS-R and PHQ ≥ 10	Mean PHQ-9 = 17 Mild = 15% Moderate = 51% Severe = 34%	Guided e-health intervention + CAU	Healthiness web-portal including psychoeducation and cognitive behavioural therapy	Complex intervention, individual therapy including web-based and mobile interventions, guided by trained advisers by telephone and e-mail, approximately 10 telephonic sessions in 6 months	307	CAU	302	49.5 (12.9)	192:417	Baseline: PHQ-9 vs. 87% ^a and 90% ^b At 12 months follow-up: 90% ^a vs. 90% ^b	PHQ-9 and reduction ≥ 5 months	Telephonic monitoring
11	Silverstone et al. (2017)	Canada	Depression, PHQ ≥ 10	Depressed cohort: Mean PHQ-9 = 15.4	E-health intervention (guidance unclear) + CAU	Cognitive behavioural therapy	MoodGYM Web-based intervention, individual therapy, patients were informed about MoodGYM, encouraged to use it and given an unique log-in number	47	No treatment	54	Not reported	Not reported	Not reported	PHQ-9	Not reported
12	Simon et al. (2011)	USA	Depression diagnosis by physician and antidepressant medication	Mean SCL = 1.84 Mild = 13% Moderate = 67% Severe = 20%	Guided e-health intervention + CAU	Care management: assessment of depressive symptoms, antidepressant medication use, and adverse effects, reasons for discontinuation	E-mail therapy, individual therapy, guided by nurse through online messaging (e-mail and chat), 4 sessions	106	CAU Stepped care CAU and usual patient provider messaging	62 32 102	45.5	58:150	Use of > 90 days: 81% ^a vs. 61% ^b	SCL	Monitoring with PHQ-9 at 2, 6 and 10 weeks
13	Depressive symptoms Hofvoldt et al. (2013)	Norway	Mild to moderate symptoms of depression: BDI-II between 10–40	Mean BDI-II = 22	Guided e-health intervention	3 modules of CBT + 1 module PST + stress reduction and relaxation techniques	MoodGYM (Norwegian-version): Web-based intervention, individual therapy, guided by psychologist, weekly face-to-face and by e-mail reminders, 5 sessions of 45–60 min (completion over 7 weeks)	52	Waiting list, treatment after 6 weeks	54	36.1 (11.3)	29:77	Baseline: 25% ^a vs. 13% ^b During trial: 25% (not specified per group)	BDI-II	Monitoring of depressive symptoms

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Table 1 (continued)

#	First author (year)	Country	Diagnostic inclusion criterion	Baseline disease severity	Intervention	Content intervention	Mode of therapy	N ^a	Control	N ^b	Mean age (SD)	Ratio M:F	Use of antidepressant medication	Main outcome	Monitoring
Anxiety disorder															
14	Nordgren et al. (2014)	Sweden	Anxiety disorder as assessed by SCID-1 and BAI ≥ 9	GAD 10% Social phobia 32% Panic disorder ± agoraphobia 31% Agoraphobia 8% Anxiety NOS 19%	Guided e-health intervention	Cognitive behavioural therapy	Bibliotherapy, individual therapy, guided by MSc clinical psychologist student, through e-mail, 7–10 sessions within 10 weeks	50	CAU	50	35.4	37:63	Baseline: 58% ^a vs. 56% ^b Increased or started medication during 12 months follow-up: 16.3% ^a vs. 3% ^b	CORE-OM	None

Anxiety NOS, anxiety not otherwise specified; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BTB, Beating the Blues; CAU, care as usual; CG, control group; CIS-R, Clinical Interview Scheduled – Revised; CORE-OM, core outcome measure; GAD, generalized anxiety disorder; GP, general practitioner; ICD-10, 10th revision of the International Statistical Classification of Diseases and Related Health Problems; IG, intervention group; PHQ-9, patient health questionnaire, 9 items; PCP, primary care physician; QIDS-SR, quick inventory depressive symptomatology, self-rated; MADRS, Montgomery Asberg Depression Rating Scale; MDD, major depressive disorder; MINI, MINI International Neuropsychiatric Interview; MSc., Master of Science; PE, physical exercise group; PST, problem-solving therapy; SCID-I, structured clinical interview for DSM disorders; SCL, symptom checklist.

* In 57% of intensified diseases management group medication was changed by the telemedicine consultation (including tele-psychiatry).

** As the main outcome was not reported, we averaged the outcomes of BDI and QIDS, to include this in the meta-analysis.

*** As the main outcome was not reported, we averaged the outcomes of MADRS and PHQ-9, to include this in the meta-analysis.

^a Intervention group.

^b Control group.

^c Intervention: Beating the Blues.

^d Intervention: MoodGYM.

^e Physical exercise control group.

^f Self-guided iCBT.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Burton 2016	+	+	+	+	+	?	+
Gilbody 2015	+	+	+	+	+	+	+
Hallgren 2015	+	?	+	+	+	?	+
Hilty 2007	+	?	?	+	?	?	?
Hoifodt 2013	+	+	+	+	+	+	+
Kessler 2009	+	+	+	?	+	+	+
Kivi 2014	?	+	+	?	+	?	+
Levesque 2011	+	+	+	?	+	?	+
Montero-Marin 2016	?	?	+	+	+	+	+
Moreno 2012	+	?	+	+	+	?	+
Nordgren 2014	+	+	+	?	+	+	+
Salisbury 2016	+	+	+	+	+	+	+
Silverstone 2017	?	+	+	?	?	?	+
Simon 2011	+	+	+	+	+	+	+

Fig. 2. Quality appraisal of included studies. Based on the Cochrane Collaboration's tool for assessing risk of bias: “+” indicates low risk of bias, “-” indicates high risk of bias, and “?” indicates unclear risk of bias.

lack of studies in the primary care setting (Nordgren et al., 2014).

4.2. Previous work

Previous systematic reviews and meta-analyses have shown that e-health interventions effectively reduce depressive and anxiety symptoms in unselected populations (Olthuis et al., 2016; Tulbure, 2011). In the present meta-analysis, however, we only found a small effect size

Fig. 3. Funnel plot of included short-term studies for depressive symptoms and disorders. The standardized mean difference (SMD) of each study (Kivi et al., 2014; Hoifodt et al., 2013; Moreno et al., 2012; Montero-Marin et al., 2016; Simon et al., 2011; Silverstone et al., 2017; Salisbury et al., 2016; Gilbody et al., 2015; Kessler et al., 2009; Burton et al., 2016; Hallgren et al., 2015) (horizontal axis) is plotted against the standard error of the SMD (vertical axis).

for e-health interventions when compared to all control groups. This contrasts with previous systematic reviews that showed moderate to large effect sizes when compared against waiting list groups (Spek et al., 2007; Richards and Richardson, 2012). In the present review, we specifically selected RCTs from primary care settings if they included participants from within the practice, and we took care to exclude RCTs of self-referred patients recruited through community advertisements. Thus, the results of this meta-analysis are more applicable to patients from primary care. The difference between our findings and those of previous research might be explained by this specific patient selection, with lower clinical effectiveness being associated with psychological interventions in primary care compared to specialist care (Cuijpers et al., 2009).

Earlier systematic reviews of anxiety disorders mostly included patients from specialist care or who were self-referred, explaining the limited number of studies of patients seeking help for anxiety disorders in primary care (Andrews et al., 2010; Arnberg et al., 2014). It is equally valid that anxiety symptoms and disorders tend to be under-recognized and undertreated in primary care, receiving less attention compared to depression (Lowe et al., 2003; Kessler et al., 1999; Kroenke Kurt, 2007). Thus, the review in anxiety cohorts was hampered not only by our strict selection criteria but also by the fact that anxiety disorders are less well studied.

Regarding cost-effectiveness, a previous systematic review for depression showed that the included e-health interventions were more likely to be cost-effective compared to control groups in 6 of 12 studies (based on a willingness to pay threshold of £20,000 per QALY gain), but that control conditions were more likely to be cost-effective in 5 of 12 studies (Paganini et al., 2018). The results of the present systematic review indicate that e-health interventions provide comparable or superior cost-effectiveness to control conditions, though the small number of included studies weaken our confidence in this comparison.

4.3. Interpretation of results

Our result indicated that e-health interventions were more effective than allowing the natural course of depression. However, we cannot exclude the possibility that the difference in effect between the waiting list and care as usual groups was accounted for by the disappointment of those in the waiting list control group at not having been allocated the intervention. Furthermore, as described in earlier studies, care as usual is not a clearly defined treatment, entailing different possible

Table 2
The clinical outcomes of the included studies.

#	Study (year)	Follow-up period	Outcome measure	% Declined participation	% Lost to follow-up	Mean change ^a /Effect size	Responders ^{a,b}	Remission	% Adherent
Depressive disorders									
1	(Burton et al. (2016)	4 wk	BDI-II QIDS-SR 16	4.60%	25%	Unadjusted BDI-II: IG: -4.2 and CG: -5.7; p = not reported QIDS-SR 16: IG: -2.7 and CG: -3; p = not reported	Not reported	Not reported	28.6%
2	Gilbody et al., 2015) and (Littlewood et al. (2015) ^c	12 wk	PHQ-9	27.30%	24%	Adjusted mean change BTB -7.6 vs. MoodGYM -7.01 vs. CAU -7.85	Response defined as PHQ-9 < 10 BTB 50% vs. MoodGYM 51% vs. CAU 56%	Remission not reported Remaining depressed PHQ ≥ 10 OR BTB vs. CAU 1.19 [0.75 to 1.88]; p = 0.46 OR MoodGYM vs. CAU 0.98 [0.62 to 1.56]; p = 0.29 OR BTB vs. MoodGYM 0.91 [0.62 to 1.34]; p = 0.69 one-sided MoodGYM non-inferior to BTB	Completed all sessions: BTB 18% vs. MoodGYM 16% Median completed sessions: BTB 2 [0–5] vs. MoodGYM 1 [0–2]
		12 mo			30%	Adjusted standard effect size (Hedges g) across all time points BTB vs. CAU -0.02 [-0.22 to 0.19]	Response defined as PHQ-9 < 10 BTB 65% vs. MoodGYM 70% vs. CAU 60%	Remission not reported Remaining depressed PHQ ≥ 10 OR BTB vs. CAU 0.77 [0.47–1.26]; p = 0.29 OR MoodGYM vs. CAU 0.56 [0.34 to 0.93]; p = 0.02 OR BTB vs. MoodGYM 0.77 [0.50–1.18]; p = 0.31	
		24 mo			33%	Adjusted standard effect size (Hedges g) across all time points MoodGYM vs. CAU 0.09 [-0.11 to 0.28]	Response defined as PHQ < 10 BTB 58% vs. MoodGYM 66% vs. CAU 61%	Remission not reported Remaining depressed PHQ ≥ 10 OR BTB vs. CAU 1.00 [0.60–1.68]; p = 0.99 OR MoodGYM vs. CAU 0.68 [0.41 to 1.15]; p = 0.15 OR BTB vs. MoodGYM 0.72 [0.47 to 1.11]; p = 0.21	
3	Hallgren et al. (2015 ; 2016) ^a	18 wk	MADRS	Not reported	21.80%	Adjusted within-group mean change IG -19.2 and PE -18.8 and CAU -12.6; all significant at p < 0.001 Adjusted between-group mean change: IG vs. CAU: 2.83 [1.47–4.19] p < 0.001 PE vs. CAU: 2.99 [1.67–4.37] p < 0.001 IG vs. CAU Hedges' g = 0.66 [0.50 to 0.82] IG vs. CAU Hedges' g = 0.46 [0.31–0.62]	Not reported	Not reported	IG: 60% (7.8 sessions out of 13) PE: 33% (12 sessions out of 36)
4	Hilty et al. (2007)	12 mo 4 mo	BDI-13	Not reported	Unclear	Not reported	IG 47% vs. PE 50% vs. CAU 47%, ns Unclear	Not reported	Mean telepsychiatric consultations: IG 4.5 vs. CG 0.5. Primary care visits: IG 9.9 vs. CG 8.4

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Table 2 (continued)

#	Study (year)	Follow-up period	Outcome measure	% Declined participation	% Lost to follow-up	Mean change**/Effect size	Responders***	Remission	% Adherent
5	Kessler et al. (2009) / Hollinghurst et al. (2010)	8 mo	BDI	Unclear	29%	Not reported	Not reported	BDI score ≤ 10 ; adjusted IG 38% vs. CG 24% At 8 months: IG 42% vs. CG 26% BDI-II score < 13 ; adjusted IG 42% vs. CG 35%; $p = 0.38$ (ns)	13% did not start 62% finished at least 5 sessions
6	Kivi et al. (2014) / Eriksson et al. (2017)	3 mo	BDI-II	Unclear	28.9%	Adjusted IG -12.27 vs. CG -11.63 (ns)	Not reported		56% completed 7 modules within 12 week treatment Mean completed modules 5.1; range 0–7 Login time: mean 248 min; range 0–868 min
		6 mo			22.20%	Intra-individual mean change in scores across time periods (0–3, 3–6 and 0–12 months) showed no significant differences between IG and CG Between group effect sizes: $d = 0.09$, $d = 0.18$ and $d = 0.09$ at 3, 6 and 12 months respectively			
		12 mo			24.40%	Unadjusted: Multiple imputation: IG -7.9 vs. CG -5.0 Complete case analysis: IG -7.9 vs. CG -4.8			
7	Levesque et al., (2011)	9 mo	BDI-II	10%	30%	Unadjusted: BDI ≤ 9 and BDI change ≥ 5 Multiple imputation: IG 38% vs. CG 22.5% Cohen's $h = 0.340$ Complete case analysis: IG 35.3% vs. CG 23.3% Cohen's $h = 0.267$	Not reported	At least 2 assessments + reports: 83.9% All 3 CTT reports: 76.2%	
8	Montero-Marin et al. (2016) / Romero-Sanchiz (2017)*	3 mo	BDI-II	4.50%	19.3%–31.4%	Guided e-health vs. CAU hedges $g = 0.08$ (unadjusted $p = 0.0634$ / adjusted $p = 0.613$) Self-guided e-health vs. CAU hedges $g = 0.12$ (unadjusted $p = 0.444$ / adjusted $p = 0.36$)	Not reported	Accessed web-based program: Guided e-health 75.0% vs. Self-guided e-health 72.4% Median completed sessions: Guided e-health 6 [0–10] vs. Self-guided e-health 4 [0–10] Completion more than 6 sessions: Guided e-health 50.0% vs. Self-guided e-health 41.8% Contacted psychotherapist: Guided e-health 11.9% vs. Self-guided e-health 0%	
		6 mo				Guided e-health vs. CAU hedges $g = 0.38$ (unadjusted $p = 0.005$ / adjusted $p = 0.004$) Self-guided e-health vs. CAU hedges $g = 0.34$ (unadjusted $p = 0.007$ / adjusted $p = 0.003$)			

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Table 2 (continued)

#	Study (year)	Follow-up period	Outcome measure	% Declined participation	% Lost to follow-up	Mean change ^a /Effect size	Responders ^{a,b}	Remission	% Adherent
9	Moreno et al. (2012)	15 mo				Guided e-health vs. CAU $g = 0.48$ (unadjusted $p = 0.003$ / adjusted $p = 0.002$) Self-guided e-health vs. CAU $g = 0.48$ (unadjusted $p = 0.001$ / adjusted $p < 0.001$) Unadjusted PHQ-9: $IG - 9.97$ vs. $IG - 7.73$; $p < 0.001$ MADRS: $IG - 13.62$ vs. $CG - 11.17$; $p < 0.001$	Response (unadjusted): $\geq 50\%$ reduction on MADRS IG 49% vs CG 34%, $p = 0.06$	Remission (unadjusted): $\geq 75\%$ reduction on MADRS IG 49% vs CG 34%, $p = 0.06$	Mean visits: IG 4.0 (SD = 2.3) vs. CAU 4.3 (SD = 3.6)
		3 mo	PHQ-9 MADRS	2%	12%				
		6 mo				Unadjusted PHQ-9: $IG - 13.47$ vs. $IG - 9.99$; $p < 0.001$ MADRS: $IG - 20.43$ vs. $CG - 13.40$; $p < 0.01$ Adjusted between-group mean difference: At 4 mo: -0.8 [-1.8 to 0.1] At 8 mo: -1.2 [-2.2 to -0.3] At 12 mo: -0.5 [-1.5 to 0.5]	IG 65% vs CG 47%, $p = 0.02$		
10	Salisbury et al. (2016)	4 mo	PHQ-9	27%	14%		IG 27% vs. CG 19%, $p = 0.019$	Adherence to antidepressant medication (scale) IG 3.9 vs. CG 3.7; $p = 0.511$	26% completed 9-10 telephonic encounters. Median encounter = 5 [IQR 2-9] Mean encounter duration 18.5 min.
11	Silverstone et al. (2017)	8 mo 12 mo 6 wk	PHQ-9	Not reported	40%	Within-group mean change on PHQ-9: e-health + CAU -12, $p < 0.001$ No treatment -11.3, $p < 0.001$ CAU -12, $p < 0.01$ Stepped care -9.9, $p < 0.05$ Between-group mean change: No statistically significant differences between four groups at 6 and 12 wk Adjusted between-group mean difference = -0.29 [-0.06 to -0.51]; $p = 0.043$	IG 30% vs. CG 23%, $p = nc$ IG 37% vs. CG 33%, $p = nc$ Not reported	Not reported	25 participants logged on < 5 participants completed > 1 session No participant completed entire program
12	Simon et al. (2011)	4 mo	SCL	6.50%	5%		IG 55% vs CG 41%, OR 1.8 [1.0–3.1]	Not reported	82% completed care management contacts. 95% at least one contact; 57% 1–2 follow-up messages; 29% 3–4 follow-up messages and 14% ≥ 5 follow-up messages
13	Depressive symptoms Hofordt et al., 2013	12 mo	BDI-II	1.50%	20.7% - 28%	Adjusted Within group effect size pre-post 7 wk IG -0.98 vs. CG -0.65 Within group effect size pre-post 6 mo IG -0.81 vs. CG -1.02 Effect size (Cohens' d) pre-post 7 wk Between group: 0.65 Effect size (Cohens' d) pre-post 6 mo between group: -0.12	Improvement IG 15.4% vs. CG 9.3%; $p < 0.01$	Remission at 6 weeks: Clinical symptoms: BDI change ≥ 8.5 and BDI ≤ 14.3 Subclinical symptoms: BDI change ≥ 4.6 and BDI ≤ 4.1 IG 32.7% vs. CG 9.3%; $p < 0.01$	60% completed all sessions 86% completed at least 2 modules. 3.8% did not start Mean completed sessions: 2.8 Mean face-to-face sessions: 7.2 Mean session time 27.2 minutes Mean duration of treatment 11.3 weeks
	Anxiety disorder								(continued on next page)

Table 2 (continued)

#	Study (year)	Follow-up period	Outcome measure	% Declined participation	% Lost to follow-up	Mean change ^a /Effect size	Responders ^{***}	Remission	% Adherent
14	Nordgren et al. (2014)	10 wk 1 year	BAI	Unclear	21% 25%	Adjusted (estimated mean) Pre-post results: mean change between groups $d = 0.58$; $p = 0.68$ Adjusted (estimated mean) Pre-1 years results: whole group: within-group $d = 0.3$ $p < 0.000$	Not reported	Not reported	32% completed all modules Mean 53.5% of prescribed modules completed. 2% did not complete any of the prescribed modules

BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BTB, Beating the Blues; CAU, care as usual; CG, control group; CIS-R, Clinical Interview Scheduled – Revised; CORE-OM, core outcome measure; GP, general practitioner; ICD-10, 10th revision of the International Statistical Classification of Diseases and Related Health Problems; IG, intervention group; PHQ-9, patient health questionnaire, 9 items; QIDS-SR, quick inventory depressive symptomatology, self-rated; MADRS, Montgomery Asberg Depression Rating Scale; MINI, MINI International Neuropsychiatric Interview; Mo, months; PE, physical exercise group; SCID-I, structured clinical interview for DSM disorders; SCL, symptom checklist; Wk, weeks.

* Three-arm 1:1 randomized controlled trial.

** Difference between baseline measurement and follow-up measurement unless stated otherwise.

*** Defined as $\geq 50\%$ reduction in outcome measure unless stated otherwise.

^aIntervention group.

^bControl group.

^cIntervention: Beating the Blues.

^dIntervention: MoodGYM.

^ePhysical exercise control group.

interventions (Kolovos et al., 2017; Watts et al., 2015). It has been described that care as usual can result in a 10% increase in remission rates compared with no treatment (Kolovos et al., 2017; Whiteford et al., 2013) and that psychological interventions add a further 15% increase in remission rates (Cuijpers et al., 2014). Among the RCTs included in the present meta-analysis, care as usual was not constrained by treatment or referral to specialist care. Most patients were treated by GPs and offered pharmacological treatment, although some received psychological treatment or were referred to specialist care.

There were no major differences in health care use between the intervention and care as usual groups, (e.g., prescription rates, psychological treatment, or referral rates). Given that psychological and pharmacological treatments were offered at high rates in both groups, we considered it reasonable to expect no major effects when e-health interventions were given alongside care as usual. Here, a floor effect might explain why we only found a small effect of e-health interventions compared to care as usual; that is, due to already lower symptom severity resulting from the additional interventions, no additional gain was expected from the addition of e-health. Because all additional treatments were offered at comparable rates in the intervention and control groups, we assume that this did not result in a biased estimate of the effectiveness of e-health.

4.4. Clinical implications

Therefore, e-health interventions could be offered before access to psychological treatment, providing an additional treatment option within primary care, and fitting within the shared decision-making process. This approach would be especially suited to patients preferring self-help approaches and who could access services online, thereby providing an alternative to pharmacological treatment and face-to-face psychological treatment. Indeed, appropriate trained primary care caregivers offering guided e-health interventions could help bridge the existing gaps between primary and specialist care and could offer a simple approach for GPs when treating patients with mild or moderate symptoms.

4.5. Strengths and limitations

To the best of our knowledge, this is the first meta-analysis to have summarized the short- and long-term effectiveness and cost-effectiveness of e-health interventions specifically for primary care. In this setting, physicians are known to diagnose and treat patients on a symptom level (i.e., based on complaints, such as anxiety or depressive symptoms), without necessarily requiring that they meet the diagnostic criteria for one of those disorders (Coyne et al., 1994; Katon and Schulberg, 1992). Patients also typically have more severe symptoms and more often fulfill the diagnostic criteria for depression or anxiety when seen in specialist care. To present a systematic review that was representative of primary care, we focused on trials among patients in that setting with depressive or anxiety symptoms or disorders. It was notable that only one study included patients based on an elevated score in a validated screening instrument (Hoifodt et al., 2013), with all other studies including patients in whom the diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 2000; American Psychiatric Association, 2013). Another strength is that we performed comprehensive searches of several data sources.

Some limitations also need to be mentioned. First, despite the heterogeneity between the different e-health interventions, such as the type of treatment (psychological or case management) and the extent of internet use, we chose to pool the data. Although this is not a limitation of the study per se, it mandates that we take care when interpreting the results. Second, given that most of the trials in our meta-analysis were for guided e-health interventions, the effectiveness and cost-effectiveness analyses are less applicable for self-guided e-health interventions.

Fig. 4. Pooled standardized mean differences of the short-term results for e-health interventions and controls when managing depressive symptoms and disorders. Short-term results are those from 4 weeks to 4 months

Fig. 5. Pooled standardized mean differences of the long-term results for e-health interventions and controls when managing depressive symptoms and disorders. Long-term results are those from 6 months to 15 months. Of note, Gilbody et al. (Gilbody et al., 2015) (de Graaf et al., 2012) reported outcomes both on 12 months and 24 months, but we only included the outcomes at 12 months in the meta-analysis. Eriksson et al. (2017) is a follow-up study of that by Kivi et al. (2014).

Fig. 6. Pooled standardized mean differences of the short-term results for e-health interventions and care as usual when managing depressive symptoms and disorders. Short-term results are those from 4 weeks to 4 months

Fig. 7. Pooled standardized mean differences of the long-term results for e-health interventions and care as usual when managing depressive symptoms and disorders. Long-term results are those from 6 months to 15 months.

Third, adherence to interventions was reported very differently across the included studies, making it difficult to interpret the effect of adherence on the reported effect sizes. Further, the quality of the included studies ranged from low to unclear to high, indicating a need to interpret the results with caution. Nevertheless, subgroup analysis (Appendix 3) of the low-, unclear-, and high-risk studies showed no

significant differences in pooled effect sizes, and the funnel plot indicated no publication bias (Fig. 2). Finally, we found just one study in patients with anxiety, precluding any meaningful conclusions on the effectiveness or cost-effectiveness of e-health interventions for this indication in primary care.

5. Conclusions

There is evidence of a small and positive effect of e-health interventions compared to care as usual for patients with depressive symptoms or depressive disorders treated in primary care. There is also promising evidence that e-health interventions might be cost-effective in the primary care setting for both depression and anxiety. Given that e-health interventions have the potential to reach a large group of patients in primary care, the small effect size could translate to major effects on health care when offered on a large scale. Nevertheless, policy makers should be prudent when implementing e-health interventions on a large scale in primary care and should instead wait for further research to confirm its cost-effectiveness in real-world settings. However, it was noteworthy that e-health interventions had a moderate effect compared to waiting to receive the studied intervention, indicating that it provides an appropriate alternative treatment for patients waiting for face-to-face psychological treatment or referral to specialist care. More studies are needed that look at patients seeking help for anxiety in primary care and that investigate the level of support and number of sessions needed to optimize guided e-health interventions.

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Conflict of interest

Co-authors BM, HB, CLHB, and MHB are involved in the conduction of a trial in this field.

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Authors' contributions

Search: BM. Reviewing and selection of studies: BM, FH, and MHB. Analyzed the data: BM. All authors contributed to and approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jad.2018.11.050](https://doi.org/10.1016/j.jad.2018.11.050).

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