Internet interventions: Past, present and future

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ABSTRACT

Internet interventions have been around now for about 20 years. While the field still suffers from a scattered terminology a large number of programs and studies exist. In the present paper I present an overview of my experiences of studying internet-supported cognitive-behaviour therapy (ICBT), but also mention other approaches including the use of smartphones. The paper covers the history of ICBT, short-term effects in controlled trials for a range of conditions, long-term effects, comparisons against face-to-face therapy, effectiveness studies, prediction studies, how the treatment is perceived, critique, and finally future directions. I conclude that we have now reached a stage in which we have numerous evidence-based treatments and procedures, and increasingly internet interventions including ICBT are disseminated.

1. Introduction

The internet is here to stay and has already changed our lives in many ways. We use the internet for numerous purposes, and in particular modern information technology, often involving the internet, has had a major impact on health care and increasingly the practice of psychological assessment and treatment (Andersson, 2016). It has also influenced health care at large, making it possible to reach patients from a distance, exchange information across the world and collect large data sets in order to monitor and improve health care services. I became involved in research using the internet at a fairly early stage and the aim of this paper is to give a perspective and view of the field of internet interventions, reflecting the life-time achievement award I received in 2017 from the International Society for Research on Internet Interventions (ISRII) (Ritterband et al., 2006). I will cover the history of internet interventions as I perceive it and comment on short and long-term effects of mainly internet-delivered cognitive behaviour therapy (ICBT). I will also address the differences between regular psychological treatment and internet interventions, comment on effectiveness studies, mechanisms of change and predictors, attitude surveys, changing formats and some critique against internet treatments. Finally, I will comment on possible future developments, bearing in mind that the future is hard to predict and that technological advancements are rapid and also dependent on cultural and economic factors.

2. History

This brief historical sketch will mainly be based on psychological treatments and how the field of internet interventions began (Andersson et al., 2016). The historical roots of internet interventions, as I view it, are mainly three. The first is the emergence of evidence-based psychological treatments, which has resulted in psychological treatments, in particular cognitive behaviour therapy (Rachman, 2015), becoming increasingly accepted as part of regular health care. The investment in association with the IAPT project in the United Kingdom is a recent example (Clark, 2011). The second historical background is the large literature on guided self-help, with numerous controlled trials, mainly using books supported by clinicians (Watkins and Clum, 2008). It has been argued that ICBT in its first version was mainly a form of bibliotherapy with some elements like e-mail support being online (Marks et al., 2007), and in many respects this is still true as most forms of internet treatment rely on text, even if the text can be read on screen. This was partly a result of early internet access being slow, not allowing multimedia and movies, and broadband access being more widely spread later on (Andersson et al., 2008a). With the advent of modern mobile phones (smartphones) the reach became even larger and for a while the internet has been possible to access from different platforms (Mohr et al., 2013). The third historical background, which has been around for a long time as well, is computerized testing and interventions (Marks et al., 1998), with early programs like Eliza (Epstein and Klinkenberg, 2001). While the focus of internet interventions research and clinical practice is often on treatment, an equally important area is...
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investigating the quality of online information (Nilsson-Ihrfelt et al., 2015). Moreover, some community members have devoted work on internet interventions including questions about the efficacy of therapist support in internet interventions (Baumeister et al., 2014), but also the constant new developments in technology including questions about the effects of serious gaming (Mohr et al., 2013) and persuasive technology (Yardley et al., 2015). Moreover, some community members have devoted work investigating the quality of online information (Nilsson-Ihrfelt et al., 2004), and also the role of web-based support groups (Griffiths et al., 2009). Much of the recent research is reflected in the journal Internet Interventions, which publish papers on various aspects of internet intervention research such as use of social media for recruitment (Thornton et al., 2016) and qualitative studies on the experiences of internet treatments (Johansson et al., 2015). The journal has existed now since 2014. There have been nine ISRII conferences, with the most recent being held in Berlin, Germany. In addition, over the last 20 years work on internet interventions has been presented at both national and international conferences outside of the field (for example at conferences on CBT).

If anything the history of internet interventions is characterized by a chaotic number of terms for describing interventions (Barak et al., 2009), with for example some using the term web-based treatment, some online therapy, and now even the term digital interventions, just to give a few examples. The choice of the term internet interventions should be credited Lee Ritterband who used it in an early review of the field (Ritterband et al., 2003b), and suggested the name for the organization back in 2004 in Stockholm at the first meeting of what later became ISRII. Of anecdotal interest could be that I had invited people for a meeting on internet and CBT, which would have been a much more narrow name for an organization.

3. Short-term effects

Usually it takes years to complete and publish the result of a randomized controlled treatment trial. Such trials are also very costly. Bearing this in mind it is close to a miracle that there are now well above 200 controlled trials on internet interventions for a range of disorders and conditions (probably 300 if unpublished work is included). This makes it a hard field to review as there are now separate reviews for conditions like depression (Karyotaki et al., 2017), chronic pain (Buhrman et al., 2016) and addictions (Riper et al., 2014), again just a few examples of studies on short-term effects. My own research in the field began with a study on headache initiated by two MSc students (Ström et al., 2000). It needs to be said that there are several active research groups doing controlled trials across the world, in particular in Australia (Titov et al., 2008), The Netherlands (van Bastelaar et al., 2011) and Germany (Ebert et al., 2014), but also various other countries like the United States (Ritterband et al., 2003a) and Switzerland (Berger et al., 2011). Early starters were the groups behind Interapy (Lange et al., 2001) and Moodgym (Christensen et al., 2004), but here I focus on the work I have been associated with. Given the special character of this paper I provide a Table on the controlled trials I have been involved in in Sweden, excluding international studies in which I have been co-worker (see Table 1). For some conditions like depression and social anxiety disorders there are more than 15 trials each, whereas for some conditions there are just one trial or even unpublished work. In addition to my work Swedish colleagues have done several additional studies, not seldom being former students of mine (Andersson et al., 2017).

Returning to Table 1 it is interesting to reflect on the outcome of all these trials. Almost all have been in the form of guided ICBT which for a long time appeared to be more effective than automated/unguided interventions (Baumeister et al., 2014). I know of studies including own unpublished work in which guidance has been in the form of “on-demand” support (Hadjistavropoulos et al., 2017), and also studies showing large treatment effects in which no support has been given during treatment but in which there has been at least some contact with clinicians and clear instructions on how to contact the researchers in cases of crisis (Titov et al., 2016). However, as stated most of our studies have included minimal clinician guidance, and overall moderate to large effects have been observed for the psychiatric conditions like depression (Andersson et al., 2005), panic disorder (Carlbring et al., 2001), social anxiety disorder (Andersson et al., 2006), generalized anxiety disorder (Paixing et al., 2011), specific phobia (Andersson et al., 2009), post-traumatic stress disorder (Ivarsson et al., 2014), health anxiety (Hedman et al., 2011), obsessive-compulsive disorder (Andersson et al., 2012a), body dysmorphic disorder (Enander et al., 2016), and eating disorders (excluding anorexia nervosa) (Strandskov et al., 2017).

When it comes to health problems findings have been mixed, much reflecting the evidence for CBT in face-to-face trials. For example, ICBT for tinnitus has consistently generated moderate large treatment effects (Andersson, 2015), and this was one of the first conditions we studied after headache (Andersson et al., 2002). It is probably also one of the first clinical implementations of ICBT with clinical service running since around year 2000 (Kaldo-Sandström et al., 2004). In addition, the effects of the Swedish program has been replicated in Germany (Weise et al., 2016) and United Kingdom (Beukes et al., 2018), with updated versions of the program. For the other health problems, results have varied from large for IBS (Ljótsson et al., 2011) to moderate for chronic pain (Buhrman et al., 2004), and somewhat smaller in the case of erectile dysfunction (Andersson et al., 2011). Overall, my impression is that the ICBT trials on psychiatric conditions have been slightly more effective than the trials on somatic problems, but again with some exceptions.

As seen in the Table we have completed studies on more trans-diagnostic problems and some other conditions. Stress is one example with one early study (Zetterqvist et al., 2005), and subsequent more recent studies showing moderate to large effects (Persson Aaplund et al., 2018). Of particular interest, and a good example of how ICBT can be seen as taking the lead, with studies not preceded by face-to-face trials, is procrastination (Rozental et al., 2015b). Trials on perfectionism (Rozental et al., 2015b) and interpersonal violence (Hesser et al., 2017) have also been published, and among the unpublished

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Conditions for which controlled studies on internet interventions have been conducted in Sweden by G. Andersson and coworkers</th>
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<tr>
<td>Somatic conditions (mainly)</td>
<td>Psychiatric and other</td>
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<tr>
<td>Headache</td>
<td>Panic disorder</td>
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<td>Tinnitus</td>
<td>Depression</td>
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<td>Cancer</td>
<td>Health anxiety</td>
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<td>Cardiac problems</td>
<td>Bulimia</td>
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<td>Erectile dysfunction</td>
<td>Generalized anxiety disorder</td>
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<td>Hearing loss</td>
<td>Pathological gambling</td>
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<td>Irritable bowel syndrome</td>
<td>Post-traumatic stress disorder</td>
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<td>Obsessive-compulsive disorder</td>
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<td>Body dysmorphic disorder</td>
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<td>Procrastination</td>
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<td>Interpersonal violence</td>
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<td></td>
<td>Perfectionism</td>
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<td>Loneliness</td>
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work we have studies on couple distress and loneliness. There are also studies on transdiagnostic treatments which includes tailored ICBT (Carlbring et al., 2010) and mindfulness (Boettcher et al., 2014a). Some of my colleagues were surprised when we started doing psychodynamic internet studies (Andersson et al., 2012c). The effects in these studies have been convincing (Johansson et al., 2013), and even if it could be argued that it is not “real” psychodynamic treatment it is based on psychodynamic theory and principles. Moreover, our trials on psychodynamic internet treatment are now included in systematic reviews on the effects of psychodynamic treatment (Fonagy, 2015).

Another example of how we embraced new developments within the field of psychological treatments is that we started running trials informed by acceptance and commitment therapy (ACT), for a range of conditions like tinnitus (Hesser et al., 2012), chronic pain (Buhrman et al., 2013), depression (Carlbring et al., 2013) and generalized anxiety disorder (Dahlin et al., 2016). In my research group we prefer to view psychotherapy “brand” as an independent variable in research, but as most of us have a background in CBT and training in that therapy form, the trials benefit from including co-workers of different therapeutic orientations.

The internet treatment format is much dependent on the treatment platform (Vlaescu et al., 2016), but once in place it can be used for other forms of interventions than psychological treatment, and I have been involved in studies on physical activity for depression (Ström et al., 2013), and exercises for stress urinary incontinence (Sjöström et al., 2013), just to give two examples. With regard to format, we have over the years done trials on smartphone-administration (Ly et al., 2014) and blended treatments (Ly et al., 2015b), and also been involved in EU-projects in this field (Kleboer et al., 2016). For some time now our platform as “responsive” in the sense that it is possible to access using different devices (Vlaescu et al., 2016).

Some overall observations can be made from running a large number of trials. First, we often collaborate with students (MSc), and in effect need to complete the trial within a few months. This speeds up the process. It would not be possible without internet recruitment, for example using social media (Thornton et al., 2016). Second, we know from psychometric studies that online administration of questionnaires work well (Hedman et al., 2010). This also saves time. However, sometimes we need to recruit participants in several waves and it is not always easy to recruit for example older persons (Silfvernæs et al., 2018). But often the sample sizes tend to be around 80–120 participants, and one trend in ICBT research is to view smaller controlled trials as “pilots” (Landgren et al., 2016), instead of running small open trials as the pilot. However, very large trials are possible and I look forward to very large trials such as one from Germany I took part in (Klein et al., 2016), with more than 1000 participants.

4. Long-term effects

In many trials on internet interventions, mostly in the form of ICBT, follow-ups have been included in the original trials or presented as separate publications. For example, it is common to report 1-year follow-up data (Rozental et al., 2017a). It is interesting to note that there now are several studies with longer follow-up than two years post treatment completion. We recently reviewed this literature, and calculated meta-analytic statistics for 14 studies involving a total of 902 participants, with an average follow-up period of three years (Andersson et al., 2018). We found long-term outcome studies on panic disorder, social anxiety disorder, generalized anxiety disorder, depression, mixed anxiety and depression, obsessive-compulsive disorder, pathological gambling, stress and chronic fatigue. The duration of the treatments was usually short (8–15 weeks) as is typical of ICBT studies. The pre-to follow-up effect size was Hedge’s $g = 1.52$ and the average symptom reduction across studies was 50%. If anything these findings are promising, but a limitation is that we have not asked carefully about subsequent treatment activities including use of the treatment techniques presented when completing ICBT. Long-term effects of ICBT delivered in regular care are also largely unknown as well as the long-term effects of less intensive and preventive forms of ICBT. Moreover, a vast majority of the studies (10/14) were from my group and colleagues in Sweden.

5. As effective as face-to-face therapy?

We were early confronted with the question if ICBT can be as effective as face-to-face CBT delivered individually or in groups. Hence, we started running such trials (Carlbring et al., 2005). These trials tended to be more difficult to run (for example as participants had to travel and be willing to be randomized to the two formats), and were often smaller than our ICBT only trials. We subsequently published a meta-analytic reviewing including the studies that had directly compared the delivery formats (Andersson et al., 2014). This review was recently updated (Carlbring et al., 2018), and we were able to include 20 studies, with a total of 1418 participants. As in the previous meta-analysis we included studies on guided ICBT for psychiatric and somatic conditions in which ICBT had been directly compared to face-to-face CBT within the same trial. In line with the first review, results showed a pooled effect size at post-treatment of Hedges $g = .05$ which clearly suggests equivalent overall effects. This is of course not the final say in this, but increasingly evidence is showing that ICBT can be as effective as other treatment formats, while still being more cost-effective (Donker et al., 2015). Thus ICBT can be a complement and also an alternative to face-to-face services. While there will always be clients in need of face-to-face treatment there are also those who prefer ICBT over face-to-face.

6. Does it work in real life?

As with the field of internet interventions in general the number of studies investigating the real-world effects of ICBT in regular clinical practice (so-called effectiveness studies) is increasing rapidly. Some very large data sets are being published (Titov et al., 2017), and from Sweden the Internet Psychiatry Unit has produced several effectiveness reports (El Alaoui et al., 2015; Hedman et al., 2014). There is no recent updated review on this topic but we published a review some years back (Andersson and Hedman, 2013) of the studies on therapist-guided ICBT. We could include 4 controlled trials and 8 open studies, involving a total of 3888 patients. Studies on panic disorder, social anxiety disorder, generalized anxiety disorder, post-traumatic stress disorder, depression, tinnitus, and irritable bowel syndrome were located. All studies suggested that it is possible to transfer ICBT to clinical practice with sustained effects and moderate to large effect sizes. As mentioned many effectiveness studies have been published since that review, but one concern is the definition of what counts are regular clinical practice and effectiveness studies (Shadish et al., 1997). If the question is if treatment works under clinically representative conditions it can also be argued that such conditions are not representative for people with the problem/disorder in the general population. Indeed, there are findings indicating that clients recruited from the general public for ICBT trials are more representative than clients seen in regular practice (Titov et al., 2010). More research is needed to investigate and describe how ICBT can be implemented successfully (Drozd et al., 2016), including planned research efforts informed by implementation science (Folker et al., 2018). In sum it appears to be the case that ICBT works in clinical practice but there are different service delivery models and examples of studies in which effects have been somewhat smaller than in the clinical efficacy trials (Kaldo et al., 2013).

7. Predictors of outcome and mechanisms of change

Arguably, given that a treatment works for at least some individuals, the first question to answer is what works for whom. This is most often
studied using observational and longitudinal approaches, but can of course be studied using experimental approaches in association with randomized trials (investigating moderators of change, for example if gender interacts with treatment outcome). Most research on predictors of outcome is usually based on data collected either before treatment starts or early on (such as early ratings of therapeutic alliance and treatment credibility). Of more theoretical (and arguably clinical) interest is the study of mechanisms of change by carefully planning and investigating mediators of change (Kazdin, 2007). Of particular interest in this form of research is the timeline and if treatment outcome can be shown to be dependent on the delivery of certain specific therapeutic components such as exposure in the treatment of anxiety disorders. This often requires intensive measurements of both the process variable and the outcome of interest, but one of the advantages of internet studies is that weekly measures can be embedded in the treatment delivery without taking time from a session or requiring therapist motivation to collect the data.

There are several studies on predictors of outcome in ICBT, and I will give examples of research I have been involved in. First, the role of demographics has been studied extensively with few consistent findings across trials. One reason could be that the inclusion and exclusion criteria in trials means that the possible predictors of outcome (negative) are not included, like for example being able to use a computer and read. Occasionally, significant predictors of outcome are reported but to the best of my understanding the literature is inconsistent (Hedman et al., 2012).

Second, there are several studies on the role of working alliance in internet treatments. Some studies report associations (Bergman Nordgren et al., 2013), but others do not (Andersson et al., 2012d). It is possible that the treatment format means that the therapeutic relationship is different and requires other measures, for example measuring alliance with the program and not just the guiding therapist (Berger, 2017).

Third, cognitive function could potentially influence the outcome of internet interventions, for example in older adults, but also in persons with depression which is known to influence cognition (Gotlib and Hammen, 2009). We have studied executive function in association with clinical trials and whereas most studies have shown no effects (Andersson et al., 2008b; Lindner et al., 2016), we did recently find an association between perseverative errors and negative outcome in a study on ICBT for older adults (Silfvernagel et al., 2018).

A fourth variable that has been investigated is genes. This research has been a fruitful collaboration across disciplines, and for example 5-HTTLPR, COMTVal158met, and BDNFVal66met genes have been studied. To date no clear associations have been established in the research I have been involved in (Andersson et al., 2013; Hedman et al., 2012), but it is possible that separate processes such as exposure may be more linked to genetic profile (Lonsdorf et al., 2010). Perhaps the most exciting findings to date on predictors of outcome I have been involved in concern brain imaging. In a research project on social anxiety disorder we first found neural correlates of change following ICBT and bias modification training online (Månsson et al., 2013a). Then we found structural changes (Månsson et al., 2016; Månsson et al., 2017), and using machine learning we were able to predict responder status as one-year follow-up (Månsson et al., 2015).

Internet interventions research has great potential in generating process data, for example using weekly measures in clinical trials and ecological momentary assessment procedures using smartphone technology (Mohr et al., 2013). There are several good examples of research on mechanisms of change and how weekly measures can be used to investigate mediators of treatment outcome (Ljótsson et al., 2013). However, more research is needed in this field and behavioural data has not been used extensively yet. Moreover, it is important to use the right statistical tools in this research as there are different trends and procedures involved.

8. How is the treatment format perceived?

There are many studies asking participants in internet trials about their treatment satisfaction and overall impressions of the treatment format (Andersson and Titov, 2014). Qualitative studies usually endorse a more open-ended approach to data collection, and there is a growing literature on experiences of internet treatments. In my own work we have for example investigated experiences of ICBT for depression (Bendelin et al., 2011), long-term memories of ICBT for social anxiety disorder (Olsson Halmetoja et al., 2014), experiences of people who drop out from treatment (Johansson et al., 2015), clients who use smartphone as delivery mode (Ly et al., 2015a), and also negative effects of ICBT (Rozental et al., 2015a).

Another type of study focus on attitudes towards the treatment format, including differences in preferences between traditional face-to-face and internet interventions (Mohr et al., 2010). I have been involved in some studies dealing with attitudes, for example internet treatments for children and adolescents (Vigerland et al., 2014), and in one EU-funded study we surveyed stakeholder attitudes towards internet treatment for depression (Topooco et al., 2017). Overall, the literature to date suggest that clients tend to be more positive than clinicians, even if there are exceptions (Wangberg et al., 2007), and that the acceptability of internet treatments tend to be very high in some groups (Wootton et al., 2011). However, when it comes to stakeholder attitudes it might still be the case that blended treatments incorporating at least some clinician contact is preferred over pure internet and self-guided interventions.

9. Critique against

With all the attention in media and in research internet interventions may of course be the subject of critique. There are also limitations that should be handled, not the least in light of the replication problem in research, with failed trials not being published (Open Science Collaboration, 2015).

First, we have the issue of trials that fail. When I started as researcher back in the early 1990s it was practically impossible to publish a failed trial, but we have now made an effort and for example published when we more or less failed to complete a trial on internet-delivered applied relaxation for women with menopausal problems (Lindh-Åstrand et al., 2015). We also published a similar “failed” trial on internet-based support for people with hearing loss (Manchaiah et al., 2014). Perhaps even more important is the need to publish trials in which the findings go against the expectations. One example, is when we delivered bias modification training for social anxiety disorder and found that there were no differences against placebo (Carlbring et al., 2012). Subsequent studies have yielded a bit more positive results (Boetetcher et al., 2013), but overall this line of research has not been as efficient as the ICBT trials with minimal therapist support and mainly text-based interventions.

Second, several studies, including a consensus report (Rozental et al., 2014), have focused on negative effects of internet interventions (Bystedt et al., 2014; Boetetcher et al., 2014a). In a large patient-level meta-analysis on deterioration we found that deterioration rates among the treated participant were 5.8% and in the controls 17.4% (Rozental et al., 2017b). Thus it is at least better to get treatment than not in terms of deterioration rates.

Finally, there have been few published arguments against internet interventions (King and Bickman, 2017), but given the large evidence-base it is not surprising if arguments will be raised if clinicians feel threatened. Our approach has always been to present internet interventions as a complement and sometimes as an alternative, but not a replacement of regular therapy services. Given the large treatment versus demand gap (Kohn et al., 2004), I am convinced there is enough work for all of us and that blended services will be more common (van der Vaart et al., 2014). Another form of critique is more directed...
towards slow implementation (Drozd et al., 2016), and the need for concerted efforts to disseminate internet interventions.

10. Future developments

The future is hard to predict, not least from a technological perspective, with changing formats and how information technology at large develops in society. Clinicians also change and new generations of clinicians may be more ready to use internet interventions as part of their services. We have done some studies on a “support system” that is not an intervention on its own, but rather a way to support clinicians in their face-to-face services (Månsson et al., 2013b). This is likely to be more common, and not only in psychological treatment but also in other forms of health care such as physiotherapy and medication. On a related note I believe other professionals than psychologists and psychotherapist will start developing internet interventions. A further likely development will be to involve clients more in the development and updating of interventions. This could be in the form of providing feedback when designing interventions or as active collaborators in the research (Dekker and Williams, 2017).

There are several research areas that are currently being investigated. One is dealing with knowledge acquisition and learning support, with findings indicating that clients improve their knowledge about their conditions and treatment including confidence in that knowledge (Andersson et al., 2012b; Strandskov et al., 2017). A second is to use machine learning (Lenhard et al., 2018) and sensor data, with the large data sets that are being generated in internet and mobile treatments (Mohr et al., 2017). A third area for the future is to conduct larger trials with recruitment from the whole world (Fairburn and Patel, 2017). Finally, we have now reached a stage when internet studies precede face-to-face studies, and a possible future development could be a reversed dissemination with knowledge from internet studies being brought to the face-to-face psychotherapy setting. One example is treatment of procrastination which first was tested in internet trials and subsequently a group treatment (Rozental et al., 2018).

11. Summary

In this paper I provided examples of the work I have been involved in over the last 20 years but also mentioned work by colleagues in the rapidly developing field of internet interventions. Progress has been fast and it is getting hard to cover the research without missing out on important work. Overall, we have now reached a stage in which we have numerous evidence-based treatments and procedures, and increasingly internet interventions are disseminated. Future research will shed more light on what works for whom but also new ways to treat problems people have.

Conflict of interest statement

I wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. I confirm that I have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing I confirm that I have followed the regulations of our institutions concerning intellectual property. I further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

I understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions, and final approval of proofs. I confirm that I have provided a correct, current email address which is accessible by the Corresponding Author.

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References


controlled trial. Diabetes Care 34, 320–325.