

The effectiveness of an online e-health application compared to attention placebo or Sertraline in the treatment of Generalised Anxiety Disorder



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ABSTRACT

Background: Generalised Anxiety Disorder (GAD) is a high prevalence, chronic disorder that can be treated effectively through a number of web-based programs. However, online web programs for GAD have not been compared to standard pharmacological treatment. The present study compares an Internet Intervention (Active Website) for GAD and a selective serotonin re-uptake inhibitor (SSRI) (Sertraline), with an online attention placebo condition (Control Website).

Objective: To evaluate the effectiveness of a web-based intervention for GAD in comparison to standard antidepressant medication and an online attention placebo condition over a 10 week period, and with a follow-up at 6 and at 12 months.

Methods: The study was part of a larger scale prevention program. 152 people aged 18–30 years who met the criteria for GAD on the MINI received referrals to the treatment sub-study. The primary outcome was anxiety symptoms measured by the Generalised Anxiety Disorder 7-item Scale (GAD-7), and the secondary outcome was depression measured by the Center for Epidemiologic Studies Depression Scale (CES-D).

Results: There was very poor uptake to the trial (around 14% of those referred). However, even in this small sample, Sertraline compared to the Control Website was significant at post-test and 6 months, and the Internet Intervention was significant at post-test. Relative to the Control Website condition at post-test, for the GAD-7 and CES-D respectively, the between group effect sizes were $d = 2.43$ and $d = 0.68$ for the Active Website condition, and 3.00 and 0.20 for the Sertraline condition. The within group effect size for the Control Website from baseline to post-test was -0.04 for the GAD-7 and 0.31 for CES-D respectively.

Conclusions: The findings will need to be extended and confirmed in a larger trial. However, they do suggest that both standard pharmacological treatment and online interventions for GAD are effective in samples with a diagnosis of GAD recruited via online methods. The low rate of engagement for face-to-face treatment by those who opt first for a web program suggests that treatment preferences are important in help-seeking.

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1. Introduction

Generalised Anxiety Disorder (GAD) is a high prevalence (Johansson et al., 2013), chronic disorder that can be treated through the web (Christensen et al., 2014a). Web-based interventions have high acceptability, are accessible, engaging and effective. Indeed, five meta-analyses published since 2009 (Andersson and Cuijpers, 2009; Andrews et al.,

2010; Cuijpers et al., 2009; Griffiths et al., 2010b; Lewis et al., 2012) confirm the effectiveness of online interventions for anxiety. For GAD in particular, strong evidence has emerged for online cognitive behavioural therapy (iCBT) (Mewton et al., 2012; Robinson et al., 2010; Spence et al., 2011). Psychodynamic online interventions have also been found to be effective (Andersson et al., 2012). Sertraline, along with the SSRIs escitalopram and paroxetine, is a first-line pharmacologic treatment for GAD (Baldwin and Polkinghorn, 2005). Randomised, placebo controlled trials have found Sertraline efficacious for GAD in adults (Allgulander et al., 2004; Brawman-Mintzer et al., 2006), children and adolescents (Rynn et al., 2001; Walkup et al., 2008) over 9 to 12 weeks, and Sertraline

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is a standard choice for GAD treatment in clinical settings. To our knowledge, a direct comparison of online therapy to a standard pharmacological intervention has not yet been reported for GAD.

We undertook a treatment trial comparing an online program (Active Website) with SSRI/antidepressant medication (Sertraline), and a control condition (Control Website). Participants were recruited to the trial after they were excluded from the primary prevention trial, an exclusion that was based on their meeting criteria for GAD during a diagnostic interview. Participants were randomised to one of three conditions: Active Website offering iCBT, Sertraline, or a Control Website. Regardless of randomised condition, all participants were assessed and monitored by medical staff during the course of the trial.

2. Methods

2.1. Study design

The study was a randomised controlled trial of young adults recruited from the Electoral Roll, who were excluded from a prevention trial (Christensen et al., 2014b), but invited to participate in a treatment trial. The study consisted of a 10 week treatment phase and a 12 month follow-up phase, with measures administered at screening, baseline, post-test, and 6 and 12 months after post-test. Unlike the prevention trial, treatment required face-to-face assessment and monitoring. The study received ethics approval from The University of Sydney (11–2009/12091) and The Australian National University (2008/548) Human Research Ethics Committees.

2.2. Study population

Adults, aged 18–30 years with a primary anxiety diagnosis of GAD formed the study population. Inclusion criteria included a GAD diagnosis based on the Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV) criteria (Brown, DiNardo, & Barlow, 1994; Sheehan et al., 1998), informed consent, access to the internet, active email address and phone number, sufficient English, willingness to attend face-to-face assessment at an inner city medical clinic attached to a University, and willingness to take antidepressant medication and to be monitored over 12 weeks. Exclusion criteria included current undertaking of cognitive behaviour therapy (CBT) with a health professional, current treatment with a psychologist or psychiatrist, risk of self-harm, psychosis, bipolar disorder, a primary diagnosis of depression, prior treatment with Sertraline, treatment with monoamine oxidase inhibitors (MOAIs), or planned pregnancy.

2.3. Recruitment procedure

A survey was sent to 120,000 randomly selected individuals aged 18–30 who were registered on the Australian Electoral Roll and located in one of five Sydney electorates (Fig. 1). Of these, 12,400 returned questionnaires, 4205 were eligible based on a score greater than 4 on the GAD-7 (Spitzer et al., 2006), and 1687 went on to complete the MINI via phone. Informed consent for the screening survey was provided in writing. Informed consent for the telephone MINI was provided verbally. Informed consent for the intervention study was provided in writing and in person at the first face-to-face meeting. Postgraduate clinical psychology students administered the telephone MINI interviews, and were blind to the participant responses to the screening survey. Interviewers were given 4 h of training, including practice interviews, with oversight from a clinical psychologist and the research team. The 152 individuals who met the criteria for GAD on the MINI interview were offered a referral to the treatment trial at the Brain and Mind Research Institute (BMRI), University of Sydney. Participants then completed further questionnaires, the ADIS-IV, and underwent a medical consultation with a general practitioner (GP) to ascertain suitability for Sertraline.

The ADIS-IV interviews were conducted by registered psychologists located at the Brain and Mind Research Institute. A total of 21 (13.9%) completed baseline and were randomised.

2.4. Baseline and randomisation

Randomisation occurred immediately after the baseline completion, using existing automated web-based software developed by the investigators. In accordance with ICH Guideline E9 (Lewis, 1999), the staff responsible for establishing randomisation procedures were not involved in the day-to-day conduct of the trial. Further, no staff members involved in the day-to-day running of the trial (i.e. not blind to group membership) were involved in conducting follow-up assessments. The research staff were not aware of group membership during the baseline assessments as randomisation occurred after this stage.

2.5. Online programs

2.5.1. Active Website

The version of the E-couch website (e-couch@anu.edu.au) used in the current study was divided into 10 modules, completed over the 10 week intervention period. The website comprises four sections including psychoeducation, cognitive behaviour therapy, relaxation and physical activity. The psychoeducation section (Modules 1 and 2) provides information on worry, stress, fear and anxiety; a description of anxious thinking; differentiation of GAD from other anxiety disorders; risk factors for GAD; comorbidity; and consequences of anxiety and available treatments. This section is based on interventions for mental health literacy that have succeeded in reducing symptoms of depression and anxiety, and improving mental health attitudes (McIntosh et al., 2004). The CBT toolkits (Modules 3–7) addressed typical anxious thoughts and included sections on dealing with the purpose and meaning of worry, the act of worrying and the content of worry. The information is derived from materials that have been found to reduce anxious cognitions in at-risk people (Kenardy et al., 2003, 2006). Progressive muscle relaxation (PMR) (Module 8) instructs participants on how to progressively tense and relax different muscle groups to induce relaxation and help to identify tension early. PMR has been trialled in a previous website program for depression in adults (Christensen et al., 2004) and adolescents (Calear et al., 2009). The mindfulness meditation module (Module 9) helps participants become aware of their breathing and body, acknowledging thoughts and external distractions but remaining focused on the present. The final module, physical activity (Module 10), tailors advice about physical activity based on the stages of change theory (Prochaska and DiClemente, 1983).

2.5.2. Control Website

HealthWatch is an online program developed for the ANU WellBeing study (Griffiths et al., 2010a). As implemented in the current study, the program provided information about various health topics each week for 10 weeks. These covered environmental health, nutrition myths, heart health, activity, medication, the effects of temperature, oral health, blood pressure and cholesterol, calcium, and back pain. Participants are also asked to respond to a number of questions about potential risk factors for anxiety. In a recent trial conducted by the Australian National University, HealthWatch was not associated with a reduction in anxiety or depressive symptoms over time, confirming its value as an attention placebo condition (Griffiths et al., 2012).

2.6. Components of trial conditions during intervention phase

All participants, regardless of condition, were provided with the same amount of exposure to the clinical team of psychologists and general practitioners (GPs). Specifically, all trial participants had scheduled appointments with a psychologist in weeks 1, 2, 5 and 10 to monitor progress and symptoms, and each participant was reviewed by a GP in

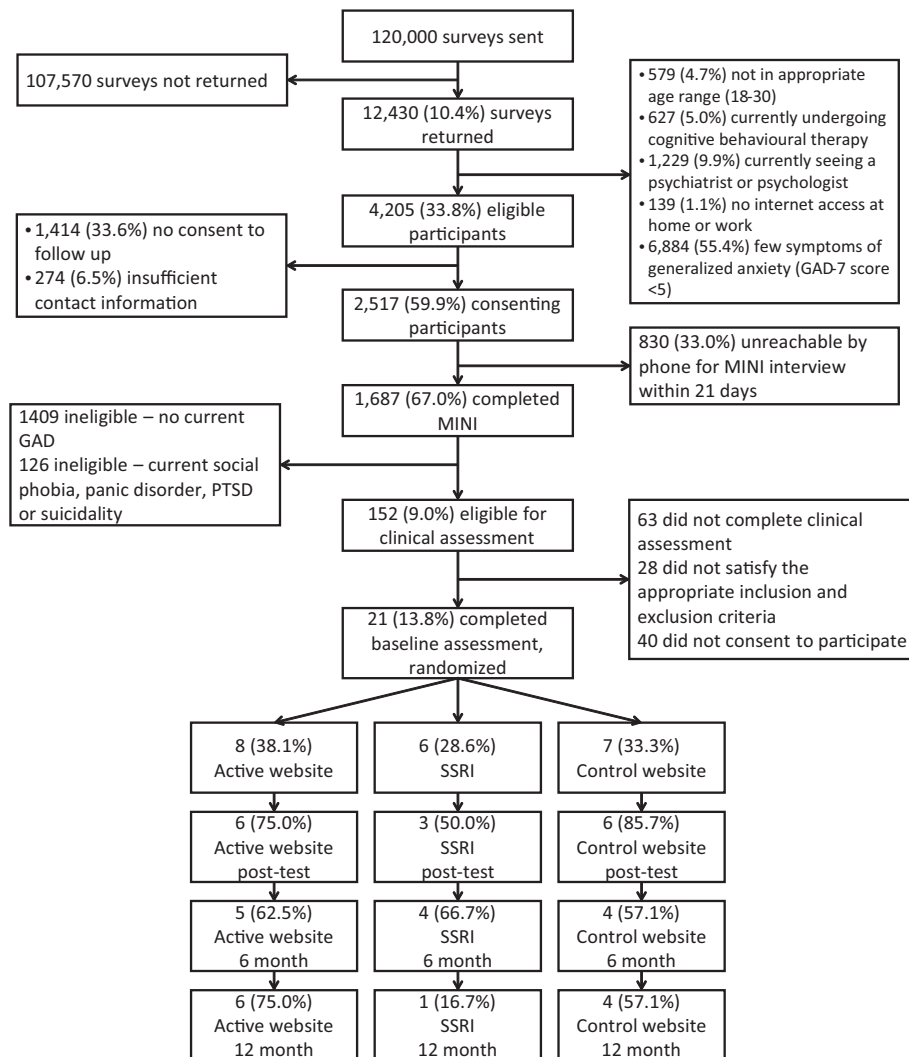


Fig. 1. Study flow. SSRI = Sertraline.

weeks 1, 5 and 10 to match the required assessments for those in the SSRI medication condition. These review sessions across conditions ensured matching for clinician/GP involvement across interventions, and active monitoring of health symptoms.

2.7. Online program conditions

In addition to the clinical team involvement, participants completed the 10 week Active Website or Control Website at their home or office outside of the clinic environment. Modules took between 30 and 60 min to complete and were deployed weekly. During face-to-face monitoring sessions in weeks 1, 2, 5 and 10, the psychologist encouraged use of the website but did not elaborate therapeutically. Participants in the Active Website condition were permitted to continue using the program after the 10 week intervention period through the public access portal.

2.8. SSRI medication condition

Participants were prescribed Sertraline for 10 weeks by the GP. Sertraline treatment was initiated at a daily dose of 25 mg which was increased to 50 mg/day after one week with good tolerability (i.e. no significant side effects). After four weeks at a daily dose of 50 mg,

participants with insufficient clinical response but good tolerability (i.e. no significant side effects) were permitted to increase their dose to a maximum of 100 mg/day. Sufficient clinical response was defined as a Clinical Global Impression Global Improvement score of 1 (Very much improved) or 2 (Much improved) (Guy, 1976). To monitor for any additional or augmented side effects which might have resulted due to this increased dosage, psychologists telephoned all trial participants during week 6 (to match for clinician contact), with additional GP appointments arranged if necessary. If participants experienced side effects that were distressing, or of which the nature and/or severity were not consistent with existing Product Information, they were withdrawn from the trial and offered alternative treatment. At the end of the 10 week intervention period, participants who had responded to treatment were given the option of continuing Sertraline either under the care of GPs at our the medical clinic or through a GP of their own choice.

2.9. Primary outcome measures

The primary outcome measure was the level of anxiety symptoms as indexed by scale scores on the GAD-7 (Dear et al., 2011; Spitzer et al., 2006) (a continuous measure). An additional outcome was the achievement of a reduction of at least 20% on this scale (a binary score).

Although it was planned, the GAD diagnosis based on the ADIS-IV was not used due to small numbers of completers.

2.10. Secondary outcome measures

The secondary outcome measure was depression as measured by the Centre for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977). Psychologists' ratings of response to treatment were also assessed using the Clinical Global Impression (CGI) rating scale (Guy, 1976).

2.11. Power

The GAD treatment trial aimed to recruit 120 participants (40 per group). However, only 21 participants were recruited, and power was restricted. Nevertheless, the present study had 88% power with these numbers to find effect sizes greater than 2 between the active and control conditions at post-test.

2.12. Statistical analyses

Given the low numbers recruited to our trial, and in contrast to our planned analyses, only two comparisons were undertaken. These were between Active Website vs Control Website and between Sertraline and the Control Website. The senior trial biostatistician was blinded to treatment group status. The GAD-7 and the CES-D data were collected blindly through the web-portal without clinician input. Primary effectiveness analyses were undertaken on an intention-to-treat basis.

Relative risk was calculated and tested for significance for categorical outcomes (achieving a 20% reduction in symptoms and the absence of DSM-IV GAD diagnoses). These outcomes were also expressed in terms of number needed to treat. Mixed effects repeated measures models estimated the effect of the intervention on anxiety and depression scores over time. These models use an intention-to-treat approach, assuming that data are missing at random. An unstructured variance-covariance matrix was assumed, with degrees of freedom estimated using Satterthwaite's correction.

3. Results

3.1. Participants

Of the 21 participants randomised, 8 were assigned to the Active Website, 6 to Sertraline, and 7 to the Control condition. Fig. 1 shows the flow of participants. Sample characteristics are presented in Table 1.

3.2. Dropout

Dropout rates are presented in Fig. 1. Dropout was greatest in the Sertraline condition, followed by the Control Website and least by the Active Website condition. These differences were not significant.

Table 1
Characteristics of the sample at baseline by trial arm.

	Active Website (n = 8)	SSRI (n = 6)	Control (n = 7)	F or χ^2	p
	Mean (SD) or %	Mean (SD) or %	Mean (SD) or %		
Age	25.0 (4.2)	23.4 (4.0)	26.0 (3.8)	0.61	0.56
% female	75	83	86	0.31	0.86
GAD-7 anxiety	11.5 (3.7)	14.8 (5.2)	11.7 (4.8)	1.12	0.35
CESD depression	23.4 (11.7)	37.0 (12.0)	27.1 (7.6)	2.92	0.08

3.3. Anxiety

Based on the mixed effects repeated measures model, there was a significant reduction in symptoms overall across the 12 month period ($F = 27.9$, $df = 3, 7.4$, $p < 0.001$), with GAD-7 scores for the whole sample decreasing from 12.5 (SD = 4.5) to 7.9 (SD = 5.4) at post-test, 7.3 (SD = 4.9) at 6 months and 4.7 (SD = 3.6) at 12 months. There was a significant condition by time interaction ($F = 5.7$, $df = 6, 7.6$, $p = 0.016$), reflecting a significant difference between Sertraline and the Control Website at post-test ($t = -5.7$, $df = 13.0$, $p < 0.001$) and 6 months ($t = -2.8$, $df = 5.8$, $p = 0.031$), and a significant difference between Active and Control websites at post-test ($t = -3.1$, $df = 12.9$, $p = 0.009$). Scores in the Sertraline group decreased from 14.8 (SD = 5.2) at baseline to 3.8 (SD = 2.8) at post-test and 5.5 (SD = 6.0) at 6 months. The effect was not significant relative to control at 12 months ($n = 1$). The Active Website was associated with a drop from 11.5 (SD = 3.7) to 6.5 (SD = 2.3) at post-test, 8.3 at 6 months (SD = 5.4) and 4.8 (SD = 4.6) at 12 months. The effect of the Active Website was not significantly different from the Control Website at 6 and 12 month follow-up. Over 12 months the Control Website was associated with no change from the baseline mean of 11.7 (SD = 4.8) to the post-test mean of 12.0 (SD = 6.5), followed by a small reduction to 8.3 (4.1) at 6 months and 5.3 (SE = 3.2) at 12 months. Planned contrasts between the Sertraline and Active Website groups revealed a significant difference of GAD-7 scores between these conditions at post-test ($t = -2.9$, $df = 13.0$, $p = 0.011$), but not at 6 or 12 months ($p = 0.107$ and 0.478 respectively). Fig. 2 takes into account attrition under the missing data at random assumption, by presenting estimated marginal means of GAD-7 scores from the mixed effects repeated measures model.

At post-test, among completers, a 20% reduction in anxiety symptoms was reached by 100% of participants in the Sertraline and Active Website conditions but only 33% of Control Website participants ($\chi^2 = 8.9$, $df = 2$, $p = .012$). DSM-IV criteria were only assessed in 8 of the participants at 6 months (3 Control, 4 Active, 1 Sertraline) using the MINI. Of these, one Control and one Active participant still met the criteria for current GAD. However, due to the small sample for which DSM-IV criteria and symptom reduction data were available, it was not possible to assess the full criteria for anxiety reduction as defined (i.e., 20% reduction and not meeting DSM-IV criteria).

3.4. Depression

CES-D scores also declined over the 12 month period ($F = 26.6$, $df = 3, 7.3$, $p < 0.001$). There was also a significant overall interaction effect between condition and time ($F = 3.7$, $df = 6, 8.3$, $p = 0.043$). Specifically, relative to the Control Website, scores in the Sertraline condition reduced significantly at 6 months ($t = -3.0$, $df = 11.5$, $p = 0.011$) and 12 months ($t = -2.4$, $df = 6.9$, $p = 0.046$) but not post-test. For Sertraline, scores were 37.0 (SD = 12.0), 19.7 (SD = 21.4), 16.0 (SD = 5.6) and 6.0 ($n = 1$) respectively. Among those who received the Active Website, scores were 23.4 (SD = 11.8), 17.7 (SD = 9.1), 20.8 (SD = 12.3) and 15.3 (SD = 13.4), respectively. The Control Website was associated with mean scores of 27.1 (SD = 7.6), 23.8 (SD = 10.6), 20.0 (SD = 9.0) and 16.5 (SD = 5.4) respectively. Fig. 3 takes into account attrition under the missing data at random assumption, by presenting estimated marginal means of CES-D scores from the mixed effects repeated measures model.

3.5. Effect sizes

Relative to the Control Website condition at post-test, for GAD-7 and CES-D respectively, the between group effect sizes were 2.43 and 0.68 for the Active Website condition, and 3.00 and 0.20 for the Sertraline condition. The within group effect size for the Control Website from baseline to post-test was -0.04 for GAD-7 and 0.31 for CES-D.

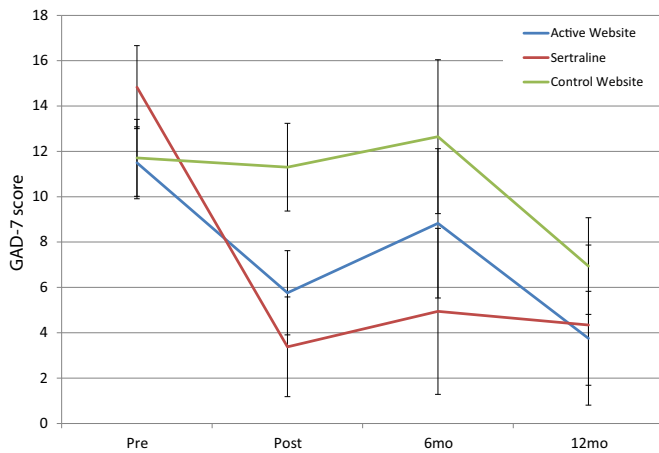


Fig. 2. Estimated marginal means from the mixed effects repeated measures model of GAD-7 scores as a function of group across measurement occasions.

4. Discussion

To our knowledge there are no registered randomised controlled trials comparing an antidepressant treatment with an online psychological intervention treatment for GAD. This trial is the first to compare an online Internet program with a gold standard pharmacological treatment.

The trial found strong effect sizes for both the Active Website and for the Sertraline for generalised anxiety symptoms as measured by the GAD 7. These effects were significant for Sertraline and the Active Website at immediate post-test, but due to the small number of participants, only Sertraline was still significant at 6 months relative to control. In addition to anxiety symptoms, a large between groups effect was found for depressive symptoms as measured by the CES-D at six months and at 12 months for Sertraline. A small, non-significant effect was found for the Active Website at post-test.

The present study is an unusual treatment study, in that recruitment to the trial was based on exclusion from a broader prevention trial, which offered an “online intervention”. The trial itself was conducted within a university based clinic, with face-to-face monitoring, and patients were required to travel distances for treatment. The final outcome measures matched those in the prevention trial, and were undertaken online through a central portal. As such, the trial has a number of important limitations, and strengths. First, recruitment from the prevention trial to the treatment trial was poor, with less than 14% of those referred to the website from the prevention arm of the project actually entering the trial. This resulted in a consequent reduction in power. However,

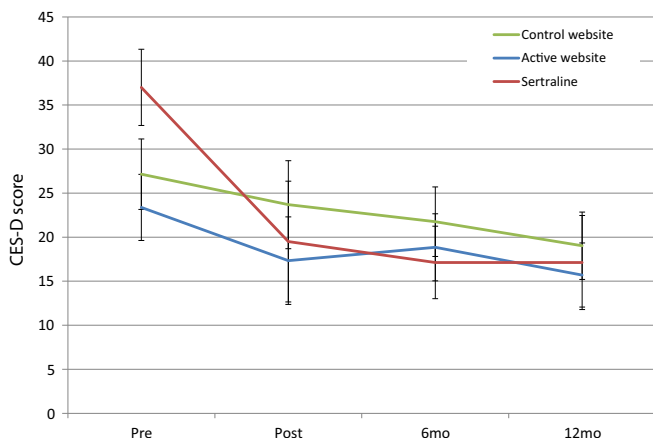


Fig. 3. CESD scores as a function of group across measurement occasions.

even with this power, the effects were large enough to yield significant effects for the Sertraline and the Active Website condition relative to Control. Importantly the effect sizes, which give an indication of the size of the effect, were large for both the Sertraline condition and the Active Website. Clearly, both of these interventions were significant.

We are unclear about why less than 14% of participants signed up to the trial. This is likely due to a mismatch between their expectations that treatment would be provided online, the burden required by the face-to-face treatment protocol, the distances needed to travel, or the negative effects of being “rejected” from the initial trial. In any case, the generalisability of the findings will be limited. We have to conclude that the final group recruited to this current trial, formed a minority prepared to accept face-to-face treatment. Nevertheless, in terms of their mental health profile relative to other groups seeking help for GAD, all met the criteria for GAD. Symptoms of GAD at baseline indicated that they were in the top 0.8% of the population, and that they represented a comparable clinical group to others used in Sertraline and face-to-face treatment trials.

Another limitation of the trial was the potential of selective bias in the findings because of differential dropout, although the dropout rate did not differ significantly. It is not clear why the Control Website participants did not improve once they were provided with the Active Website at post-test. This may be due to the fact that increased wait times decrease treatment effectiveness, or that participants sought ineffective interventions elsewhere. Due to the number of clinicians and research staff involved, the implementation of trial protocol may not have been uniform over the course of recruitment, which spanned two years. Finally, despite the recent recognition of the importance of negative effects (Rozenal et al., 2014), it was not possible to meaningfully examine these outcomes, another limitation of the small sample size.

The trial did have a number of strengths. First, the clinical outcomes used in the trial were all collected in an automated fashion, via the web portal, increasing level of blinding. The original sample was recruited via the Electoral Roll, so participants may have included those who would not normally seek treatment, and thus may have represented those with ‘unmet need’, and indeed, may have represented a group who were reluctant to seek treatment.

Although small, the study suggests that GAD is responsive to both online treatment and Sertraline, a finding that requires extension and replication. The outcomes of the present trial are relevant to the practical management of GAD in primary care. GAD treatment using an e-health application with minimal therapist input appears to be effective, and as such, offers an alternative to medication, and may be a preferred treatment. Given the shortage of qualified therapists, escalating health costs, and the low rates of treatment seeking in those with a mental disorder (Wittchen, 2000), these findings have important clinical and practical implications. There is also evidence emerging that CBT in combination with an SSRI may be helpful in general practice for patients with treatment resistant depression (Wiles et al., 2013), suggesting a possible area of further investigation.

From a research perspective, it has been questioned whether online patients are as severe or incapacitated as offline patients. This study goes some way to confirming that these patient groups comprise similar clinical profiles, and also that for some, online treatment may be preferred to medication in a GP setting.

The effect sizes reported for the GAD effects in this study were large. Many online programs do not report within-group effects of such magnitude. The effects of Sertraline are often reported to be much less. There are a number of possible explanations for the size of these effects. First, the Active Website and Sertraline were offered in the context of best practice treatment, with regular follow-up by psychologists and GPs. Second, by the time participants reached the treatment stage of the trial, and were enrolled in it, their commitment and motivation were likely to be high. An additional observation is that the provision of GP and psychologist support alone was not effective, given the very weak effects observed in the Control Website condition.

Competing interests

KMG is the Director of e-hub at the ANU which offers the E-couch program through an open access portal. However, KMG derives no personal financial benefit from the operation of e-hub.

Authors' contributions

HC, AJG, AJM, KMG, PJB, JK and IBH developed the trial protocol and CE, PB, KK and KB further developed the details of the trial protocol. AJG and IBH supervised the trial. BOD collated the clinical data. CE and KK assisted with the data collection. HC drafted the manuscript and interpreted the data. PB undertook the data analysis. All authors contributed to the editing of the manuscript.

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