Chapter 6

Low-intensity treatment for panic symptoms – A pragmatic randomised controlled trial of an internet-based guided self-help intervention

Submitted:
Abstract

Background
Internet-based guided self-help is efficacious for panic disorder (PD), but it is not known whether such treatment is effective for milder panic symptoms as well.

Objectives
To evaluate the effectiveness of Don’t Panic Online, an internet-based self-help course for mild panic symptoms, which is guided by email.

Methods
A pragmatic randomised controlled trial was conducted. Participants (n = 126) were recruited from the general population and randomised to either the intervention group or to a waiting-list control group. Inclusion criteria were a PDSS-SR score of 5-15 and no suicide risk. Panic symptom severity was the primary outcome measure, secondary outcome measures were anxiety and depressive symptom severity. Measurements took place at baseline and 12 weeks after baseline.

Results
Analyses of covariance (intention-to-treat) showed no significant differences in panic symptom reduction between groups. Completers-only analyses revealed a moderate effect size in favour of the intervention group (d = 0.73, P = .012). Only 27% of the intervention group finished lesson 4 or more (out of 6). Non-responds at T1 was high for the total sample (42%). Diagnostic interviews showed that many participants suffered from comorbid depression and anxiety disorders.

Conclusions
The internet-based guided self-help course appears to be ineffective in individuals with panic symptoms. However, intervention completers did derive clinical benefits from the intervention.

This trial has been registered in the Netherlands Trial Register (NTR1639). The Netherlands Trial Register is part of the Dutch Cochrane Centre.
Introduction

Panic disorder (PD) with or without agoraphobia is a prevalent anxiety disorder associated with substantial loss of quality of life for the patient and considerable costs to society (Batelaan, De Graaf, Van Balkom, Vollebergh, & Beekman, 2007; Batelaan, Smit, et al., 2007; Bystritsky, et al., 2010; Taylor, 2006). Just as prevalent is subclinical PD (Batelaan, De Graaf, et al., 2007; Bystritsky, et al., 2010), which can be defined as panic symptoms that do not meet full DSM-IV criteria for PD. Subclinical panic symptoms can develop into clinical PD and are also a predictor for the development of mental disorders other than PD, such as generalised anxiety disorder, social phobia or major depressive disorder (MDD) (Kinley, Walker, Emns, & Sareen, 2011).

PD can be effectively treated with psychological or drug therapy (Furukawa, Watanabe, & Churchill, 2006; Sanchez-Meca, Rosa-Alcazar, Marin-Martinez, & Gomez-Conesa, 2010; Schmidt & Keough, 2010). Research indicates that it is also possible to prevent or delay the onset of clinical PD in people with subclinical panic symptoms (Gardenswartz & Craske, 2001; Meulenbeek, et al., 2010). A recent study showed that a group intervention mainly involving cognitive behavioural therapy effectively reduces symptoms in subclinical cases of PD, as well as in relatively mild cases (Meulenbeek, et al., 2010). This group course could also be acceptable from a cost-effectiveness point of view (Smìt, et al., 2009).

Internet-based guided self-help has shown to be an efficacious treatment of PD as well, with a large effect size (Hedge’s $g = 0.83$) (Andrews, Cuijpers, Craske, McEvoy, & Titov, 2010). To date, all but one study (Silfvernasel, et al., 2012) comparing internet-based guided self-help for PD with a control condition have focussed purely on groups with clinical PD, which, commonly, also had to be the primary diagnosis (e.g., Carlbring, et al., 2006; Klein, Richards, & Austin, 2006). These studies excluded subclinical cases (e.g., Carlbring, et al., 2006; Klein, et al., 2006; Wims, Titov, Andrews, & Choi, 2010). Recently, an internet-based version of the group course Don’t Panic has been developed. This intervention, Don’t Panic Online (DPO), is an internet-based self-help course with minimal guidance, specifically for individuals with mild panic symptom severity. The aim was to provide an accessible, low-intensity, early intervention for panic symptoms.

The current study is a pragmatic randomised controlled trial (RCT) of the effectiveness of DPO in reducing panic and anxiety symptoms among participants with subclinical and mild clinical PD. We postulate a difference in effect between DPO and a waiting-list control group.
Method

Design
We conducted a pragmatic RCT with two arms: (a) internet based guided self-help, (b) a waiting-list control group (see below). The Medical and Ethical Committee of VU University Medical Centre approved the study protocol, which is described in greater detail in Chapter 5.

Study population
We included participants aged 18 and above, with subclinical PD or clinical PD with relatively mild symptom severity, and access to the internet. Any individuals who were at risk of suicide were excluded. Subclinical or mild PD was defined as having a score of 5 to 15 on the Panic Disorder Severity Scale-Self Report (PDSS-SR) (Houck, Spiegel, Shear, & Rucci, 2002). These cut-off points represent slight to moderate panic symptom severity (Furukawa, et al., 2009). No restrictions were imposed on the use of pharmacotherapy or psychotherapy.

Sample size
Previous RCTs of internet-based self-help interventions for panic symptoms showed large between-group effect sizes (Andrews, et al., 2010). Our aim was to recruit participants with milder symptom severity than those who took part in these studies. Therefore, our sample was expected to show a smaller decrease in panic symptoms. Based on a moderate effect size (Cohen's $d = 0.50$), and using a two-sided t-test ($\alpha = 0.05$, power 80%) to compare the PDSS-SR scores of the intervention group with those of the control group, we aimed to include 128 participants (Cohen, 1988), with 64 in each group. Any missing values at post-treatment were imputed.

Recruitment
Participants were recruited from the general population. Most of those who applied for participation did so after reading about this study in the health section of an online newspaper. Additional online recruitment was conducted by means of a Facebook advertising campaign and by posting messages on panic-related or anxiety-related message boards. This was supplemented by 'offline' recruitment by means of advertisements in national newspapers and articles in local newspapers. Interested individuals were directed to a study website, where they could find information about participation, and a downloadable informed consent form. The application procedure involved printing and signing the informed consent form,
then sending this to the research team (either as a physical document, by conventional mail, or as a scanned document attached to an email).

**Randomisation and procedure**

Consenting applicants were sent an email with a link to the online questionnaires. The baseline (T0) questionnaires included the screening questionnaires for inclusion. Any participants who reported severe panic symptoms or who were at risk of suicide were sent an automatic message advising them to contact their general practitioner and/or to visit a website for suicide prevention. This website (www.113online.nl) offers psycho-education and a help-line by telephone or online chat (Mokkenstorm, Huisman, & Kerkhof, 2012). Those participants who had completed T0 and who met the inclusion criteria were contacted within two weeks for a diagnostic interview by telephone. This interview was used to obtain a more detailed overview of the study sample, not for the purposes of inclusion or exclusion. After the interview, all participants were randomised to one of the two groups. Randomisation was stratified for the presence or absence of agoraphobic symptoms (PDSS-SR item 4 score 2 or higher) and the use of antidepressants or sedatives. Randomisation lists were generated automatically, using a computer program. The T0 measurement can be considered to be double blind, as the participants were not randomised until they had completed all of the questionnaires and the diagnostic interview. Blinding of the participants at post-treatment assessment (T1) was not possible, as at that stage they were aware of the nature of the group to which they had been allocated. T1 was scheduled twelve weeks after the baseline assessment. Both T0 and T1 were self-report and were conducted through the internet. Any participants who had not completed T0 or T1 were sent up to three automated reminders by email, at weekly intervals.

**Intervention**

Don’t Panic Online (DPO) is a guided, internet-based, individual, self-help course, based on cognitive behavioural therapy principles. The course consists of six sessions, in which the participants learn to control their panic symptoms by applying various cognitive and behavioural techniques and skills. The course’s content is described in more detail in Chapter 5. A typical lesson takes about thirty minutes and consists of an introduction, a discussion of the previous lesson’s homework, new theory and homework for the following week. A track-and-trace system keeps a record of the dates on which participants log on and complete a lesson. The participants in the intervention group were coached by trained, Master’s-level Clinical Psychology students. Every week, these participants
received an email from their coach, asking how they were doing and whether they were experiencing any difficulty in following the programme. The coaches responded to questions about the course and the associated exercises. They also gave brief replies to questions about the participant's mental health. The coaches were supervised by the first author. On average, the total time spent on each participant was one to two hours.

Participants in the control group received access to DPO after completing the T1 measurement (12 weeks after T0). While waiting, they had access to an information website about the symptoms of panic and agoraphobia. This website included advice to contact a general practitioner, in case the participant had further questions about panic symptoms and its treatment. All of the participants in the control group and the intervention group were free to seek any (additional) help they might require.

**Instruments**

The following variables were measured: demographic data, DSM-IV diagnosis, symptoms of anxiety and panic, depressive symptoms, and suicide risk. All variables were measured at both T0 and T1, except for demographic data, diagnosis and suicide risk, which were only measured at T0.

The T0 measurement started with demographic questions. These included age, gender, place of birth, marital status, education level, physical health, and previous mental health diagnoses.

The Composite International Diagnostic Interview (CIDI) 12-month prevalence (Robins, et al., 1988) was used to ascertain the presence or absence of PD, other anxiety disorders, and depression. A clinical diagnosis was made, not as an inclusion criterion, but to gain a more complete overview of the participants. The CIDI, which was developed by the World Health Organisation, is an extensive, fully structured diagnostic interview to assess DSM-IV Axis-I diagnoses (Robins, et al., 1988). The only subscales used were depression, PD, agoraphobia, generalised anxiety disorder, social phobia and post-traumatic stress disorder. In this study, a trained interviewer administered the CIDI by telephone.

The severity of current panic symptoms was measured using the Panic Disorder Severity Scale - Self Report (PDSS-SR). The PDSS, which was originally designed as a face-to-face interview for both research and clinical practice (Shear, et al., 2001), was adapted to be used in a patient self-report format (Houck, et al., 2002). The instrument contains seven items that assess the severity of seven dimensions of PD and its associated symptoms. The PDSS-SR generates a total score ranging from 0 to 28. The higher the score, the more severe the panic
symptoms. The questionnaire has adequate psychometric properties when compared with the PDSS (Houck, et al., 2002; Wuyek, Antony, & McCabe, 2011). For the purposes of the current study, a score of less than 5 is taken to indicate that there are no clinically significant symptoms, while a score of more than 15 is interpreted as severe PD. Our study, therefore, focuses on the group with scores ranging from 5 to 15. According to the study by Furukawa et al. (Furukawa, et al., 2009), this score range identifies participants with mild to moderate panic symptoms, but excludes those without panic symptoms, as well as those with severe panic symptoms.

Anxiety symptoms in general were measured using the Beck Anxiety Inventory (BAI) (Beck, Epstein, Brown, & Steer, 1988). The BAI contains 21 short questions. Convergent and divergent validity is sufficient (De Beurs, Wilson, Chambless, Goldstein, & Feske, 1997; Lykke, Hesse, Austin, & Oestrich, 2008). The score ranges from 0 to 63. A score of 30 or above is considered to correspond to severe anxiety symptoms.

Depressive symptoms were measured using the CES-D (Radloff, 1977). The CES-D is a 20-item self-report questionnaire. The score of each individual item ranges from 0 to 3, while the total score ranges from 0 (no feelings of depression) to 60 (severe feelings of depression). Convergent validity of the online Dutch version for adults with other depressive measures is good (Donker, Van Straten, Marks, & Cuijpers, 2010). With a cut-off score of 22 for MDD, it also has good predictive validity (Donker, et al., 2010).

Suicide risk and suicidal ideation were measured using the specific section of the Mini-International Neuropsychiatric Interview (MINI) (Lecrubier, et al., 1997; Sheehan, et al., 1998). The MINI suicide section consists of six items and classifies participants into categories ranging from no suicide risk to high suicide risk. Any individuals with a moderate to high suicide risk were excluded from this study. In the current study, these items were administered online and presented as self-report items.

An indication of health care services usage during the past month was obtained using Part I of the Trimbos and Institute of Medical Technology Assessment Questionnaire on Costs Associated with Psychiatric Illness (TiC-P) (Hakkaart-van Roijen, Van Straten, Donker, & Tiemens, 2002).

Finally, the 71 battery of online questionnaires included open questions concerning the participant’s subjective experience with DPO and reasons for not finishing the programme. These questions were only administered to the intervention group.
Figure 1. Flow chart.

Assessed for eligibility ($n = 368$)

- Excluded ($n = 242$)
  - Double applications ($n = 5$)
  - Did not complete baseline questionnaires ($n = 61$)
  - Did not meet inclusion criteria ($n = 105$)
    - Too light panic symptoms
    - 40 too severe panic symptoms
    - 37 suicide risk (in 13 cases combined with too mild or too severe panic symptoms)
  - Did not consent to a diagnostic interview or could not be contacted by the interviewer ($n = 50$)
  - Withdrew ($n = 11$)
  - Other reasons ($n = 12$)

Randomised ($n = 126$)

Allocated to Don't Panic Online ($n = 63$)
- Received allocated treatment at least partially ($n = 60$)
- Did not log in ($n = 3$)

Allocated to waiting list ($n = 63$)
- Logged on to the information website ($n = 53$)
- Did not log in ($n = 10$)

Completed lesson 1 ($n = 40$)
Completed lesson 2 ($n = 32$)
Completed lesson 3 ($n = 30$)
Completed lesson 4 ($n = 27$)
Completed lesson 5 ($n = 5$)
Completed lesson 6 ($n = 0$)

Completed T1 ($n = 34$)

Analysed ($n = 63$)

Completed T1 ($n = 39$)

Analysed ($n = 63$)
Analyses

Firstly, means and standard deviations were calculated for the variables age, and symptom severity of panic, anxiety and depression. Any differences in symptom severity between the intervention group and control group were expressed in terms of Cohen's $d$ (see below) to give an indication of the magnitude of the difference in question.

Between-group effects at $T1$ were calculated using analyses of covariance (ANCOVA), controlling for pre-treatment scores. Effect sizes on continuous measures were expressed in terms of Cohen's $d$, which was calculated by subtracting one mean score from the other, and dividing the mean difference thus obtained by the pooled standard deviation. Effect sizes of 0.8 can be assumed to be large, while effect sizes of 0.5 are moderate, and effect sizes of 0.2 are small (Cohen, 1988). As Cohen's $d$ does not take covariance into account, partial $\eta^2$ is also reported in this paper. It cannot be estimated which level of partial $\eta^2$ could be considered adequate, because this effect size is dependent on several factors. Within-group effects were analysed using paired-sample $t$-tests, and expressed in terms of Cohen's $d$, where the correlation between $T0$ and $T1$ was taken into account by applying Morris & DeShon's equation 8 (Morris & DeShon, 2002).

Finally, the proportion of participants below the PDSS-SR cut-off points for clinical and subclinical PD was calculated for both $T0$ and $T1$. We used the cut-off points of 8 and 5, the former indicating clinical PD (Shear, et al., 2001) and the latter subclinical PD (Furukawa, et al., 2009). Participants with scores below 5 were considered to be symptom-free. All analyses were conducted for the full sample, for the subgroup completers, and for subgroups with and without the diagnosis of PD according to the CIDI. We maintained a two-sided $\alpha$ of .05. SPSS version 17 was used for all analyses.

The data were analysed in agreement with the intention to treat (ITT) principle. Missing data at $T1$ were imputed by multiple imputation, where, except for nominal variables, all variables (i.e. age, education level, clinical diagnoses and symptom severity on all measures at $T0$ and $T1$) were included as predictors. Ten datasets were generated and analyses were performed using pooled data. Compared with single imputation methods, multiple imputation generates a more conservative estimate of the sample standard error (Donders, Van der Heijden, Stijnen, & Moons, 2006) and overestimation of effect sizes and $P$-values is unlikely. For the purpose of sensitivity analysis, $P$-values and effect sizes were also estimated by running the Expectation Maximisation (EM) algorithm (Little & Rubin, 2002) on the missing data.
Table 1. Baseline data.

<table>
<thead>
<tr>
<th></th>
<th>Total sample n = 126</th>
<th>Intervention group n = 63</th>
<th>Control group n = 63</th>
<th>Difference at baseline (Cohen’s d)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td>mean (sd) / n(%)</td>
<td>mean (sd) / n(%)</td>
<td>mean (sd) / n(%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>36.6 (11.4)</td>
<td>36.7 (12.2)</td>
<td>36.4 (10.7)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>85 (67%)</td>
<td>44 (70%)</td>
<td>41 (65%)</td>
<td></td>
</tr>
<tr>
<td>Born in the Netherlands</td>
<td>115 (91%)</td>
<td>57 (90%)</td>
<td>58 (92%)</td>
<td></td>
</tr>
<tr>
<td>Living alone</td>
<td>50 (40%)</td>
<td>23 (37%)</td>
<td>27 (43%)</td>
<td></td>
</tr>
<tr>
<td>High education*</td>
<td>63 (50%)</td>
<td>30 (48%)</td>
<td>33 (52%)</td>
<td></td>
</tr>
<tr>
<td>Physical health problems</td>
<td>9 (7%)</td>
<td>5 (8%)</td>
<td>4 (6%)</td>
<td></td>
</tr>
<tr>
<td>Previsously diagnosed with a mental disorder</td>
<td>47 (37%)</td>
<td>22 (35%)</td>
<td>25 (40%)</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnoses</strong></td>
<td>n*** (%)</td>
<td>n(%)</td>
<td>n(%)</td>
<td></td>
</tr>
<tr>
<td>PD with agoraphobia</td>
<td>61 (49%)</td>
<td>30 (48%)</td>
<td>31 (50%)</td>
<td></td>
</tr>
<tr>
<td>PD without agoraphobia</td>
<td>36 (29%)</td>
<td>17 (27%)</td>
<td>19 (30%)</td>
<td></td>
</tr>
<tr>
<td>Agoraphobia without PD</td>
<td>17 (14%)</td>
<td>10 (16%)</td>
<td>7 (11%)</td>
<td></td>
</tr>
<tr>
<td>GAD</td>
<td>11 (9%)</td>
<td>5 (8%)</td>
<td>6 (10%)</td>
<td></td>
</tr>
<tr>
<td>Social phobia</td>
<td>78 (63%)</td>
<td>39 (63%)</td>
<td>39 (63%)</td>
<td></td>
</tr>
<tr>
<td>PTSD</td>
<td>16 (13%)</td>
<td>4 (6%)</td>
<td>12 (19%)</td>
<td></td>
</tr>
<tr>
<td>MDD</td>
<td>53 (43%)</td>
<td>27 (44%)</td>
<td>26 (42%)</td>
<td></td>
</tr>
<tr>
<td><strong>Symptom severity</strong></td>
<td>mean (sd)</td>
<td>mean (sd)</td>
<td>mean (sd)</td>
<td></td>
</tr>
<tr>
<td>Panic (PDSS-SR)</td>
<td>8.9 (3.0)</td>
<td>8.8 (3.2)</td>
<td>9.1 (2.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>Anxiety (BAI)</td>
<td>24.9 (10.8)</td>
<td>23.7 (10.2)</td>
<td>26.0 (11.3)</td>
<td>0.22</td>
</tr>
<tr>
<td>Depression (CES-D)</td>
<td>20.8 (9.0)</td>
<td>20.0 (9.1)</td>
<td>21.6 (9.0)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*Defined as the equivalent of a bachelor’s degree or higher.
**Percentages add up to more than 100% due to comorbid diagnoses.
***Missing data of 2 participants, n = 124.

Results

Sample

Of 368 applicants who applied and sent in informed consent forms, 126 were included in the study. See Figure 1 for a flow chart and an overview of excluded applicants. The participants were mainly female (67%), had been born in the Netherlands (91%), with a mean age of 36.6 (range 18-67, SD = 11.4) and 50% had
undergone higher education (Table 1). Diagnostic interviews showed that 97 (78%) of the included participants met the criteria for panic disorder (PD) with or without agoraphobia. Other DSM-IV anxiety disorders and MDD were also prevalent (Table 1). Five participants (4%) did not meet the criteria for a diagnosis of a mood or anxiety disorder. The control group had slightly higher baseline scores than the intervention group (Table 1), but there were no to little further differences between the intervention group and control group. Details of health care services usage, e.g., visits to the general practitioner, are given in Table 4. About half of the participants reported having consulted a general practitioner in the month immediately prior to the study, and one third had seen a psychologist or psychiatrist.

**Study drop-out**

The post-treatment measurement was completed by 73 participants (58%). There was no significant difference between the measurements and characteristics of these 73 study completers and those of the 53 participants who were lost to follow up. However, within the intervention group, study drop-outs were less likely to have completed lessons 1 to 4 of the course ($\chi^2 = 15.11$, $P < .001$).

**Intention to treat analyses**

After multiple imputation, analyses of covariance showed no significant difference in panic symptom severity at $T1$ between groups as measured by the PDSS-SR ($t = -1.17$, $P = .246$, partial $\eta^2 = .023$, Cohen’s $d = 0.30$; Table 2). The within-group difference of the intervention group was significant ($t = 3.06$, $P = .007$, $d = 0.62$), as was the within-group difference of the control group, albeit with a smaller effect size ($t = 2.26$, $P = .033$, $d = 0.40$). The mean BAI score, too, did not differ between groups ($t = -1.71$, $P = .087$, partial $\eta^2 = .027$, $d = 0.39$; Table 2). Nor were there any differences between groups in terms of depressive symptoms, as measured by the CES-D ($t = -1.56$, $P = .123$, partial $\eta^2 = .034$, $d = 0.39$; Table 2).

At $T1$, and with missing values imputed, 24 participants (38%) in the intervention group and 13 (20%) in the control group had PDSS-SR scores of less than 5, i.e. symptom free. This difference did not reach significance ($\chi^2 = 5.70$, $P = .117$). With regard to the cut-off point of 8 (the recommended cut-off for clinical diagnosis), 28 participants (44%) in the intervention group and 22 (35%) in the control group scored below 8 at $T0$. At $T1$, 38 participants in the intervention group (60%) and 33 participants in the control group (52%) scored below 8, a non-significant difference ($\chi^2 = 1.34$, $P = .53$).

Sensitivity analyses with the EM algorithm gave slightly different results. There was no significant effect between groups on the primary outcome measure.
(PDSS-SR: $t = -1.79$, $P = .076$, partial $\eta^2 = .025$, $d = 0.34$), but the difference in BAI anxiety symptoms did reach significance ($t = -2.33$, $P = .022$) with a moderate effect size ($d = 0.46$, partial $\eta^2 = .042$). CES-D depressive symptoms also differed between groups ($t = -2.69$, $P = .008$) with a moderate effect size ($d = 0.47$, partial $\eta^2 = .055$).

Table 2. Differences between groups at $T1$, intention to treat ($n = 126$). Missing data imputed by multiple imputation.

<table>
<thead>
<tr>
<th></th>
<th>Intervention group ($n = 63$)</th>
<th>Control group ($n = 63$)</th>
<th>Between-groups effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>sd</td>
<td>mean</td>
</tr>
<tr>
<td>PDSS-SR</td>
<td>5.8</td>
<td>4.9</td>
<td>7.3</td>
</tr>
<tr>
<td>BAI</td>
<td>17.0</td>
<td>12.7</td>
<td>22.0</td>
</tr>
<tr>
<td>CES-D</td>
<td>16.4</td>
<td>12.3</td>
<td>21.1</td>
</tr>
</tbody>
</table>

*Controlling for symptom severity at $T0$.

Table 3. Differences between groups at $T1$, completers* ($n = 57$).

<table>
<thead>
<tr>
<th></th>
<th>Intervention group ($n = 16$)</th>
<th>Control group ($n = 39$)</th>
<th>Between-groups effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>sd</td>
<td>mean</td>
</tr>
<tr>
<td>PDSS-SR</td>
<td>4.6</td>
<td>3.3</td>
<td>7.5</td>
</tr>
<tr>
<td>BAI</td>
<td>15.6</td>
<td>13.4</td>
<td>22.6</td>
</tr>
<tr>
<td>CES-D</td>
<td>12.1</td>
<td>8.5</td>
<td>21.6</td>
</tr>
</tbody>
</table>

*Control group completers are those who provided post-treatment data. Intervention group completers are those who provided post-treatment data and completed at least lesson 4.

**Controlling for symptom severity at $T0$.

Completers-only analyses
Those participants in the intervention group who had completed the first four lessons (or more) of the course ($n = 17$) were included in the completers-only analyses. Sixteen of the 17 participants in the intervention group who had completed the first four lessons also filled in $T1$ questionnaires. Accordingly, there were 16 completers in the intervention group. These 16 individuals did not significantly differ from the non-completers in the intervention group at $T0$ in
terms of age, education, clinical diagnosis and symptom severity. Control group 'completers' were those who filled in T1 \((n = 39)\).

Analyses of covariance showed significant differences between the intervention group completers and control group completers with regard to panic symptom severity at T1 \((t = -2.60, P = .012, d = 0.73\); see Table 3), in favour of the intervention group. The intervention group was also characterised by a large within-group effect on panic symptoms \((t = 4.92, P < .001, d = 1.23\). In the control group, within-group effects did not reach significance. Analyses of covariance also showed that BAI anxiety symptom severity differed significantly between groups \((t = -2.37, P = .021, d = 0.60, \text{see Table 3}\), as did depressive symptom severity, as measured using the CES-D \((t = -2.52, P = .015, d = .94\).

Ten (68\%) of the intervention completers and 8 (21\%) of the control group completers had a PDSS-SR score of less than 5 at T1, which is a significant difference \((\chi^2 = 9.09, P = .004)\). In terms of the cut-off point for clinical diagnosis, 13 participants in the intervention group (81\%) and 23 (59\%) in the control group scored less than 8. This difference did not reach significance \((\chi^2 = 2.49, P = .134)\).

Lastly, health care service usage rates did not differ, either within or between groups (see Table 4).

<table>
<thead>
<tr>
<th></th>
<th>T0 Intervention group ((n = 63))</th>
<th>Control group ((n = 63))</th>
<th>T1* Intervention group ((n = 16))</th>
<th>Control group ((n = 39))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visited general practitioner (%)</td>
<td>27 (43%)</td>
<td>31 (49%)</td>
<td>2 (13%)</td>
<td>12 (31%)</td>
</tr>
<tr>
<td>Visited psychologist or psychiatrist (%)</td>
<td>23 (37%)</td>
<td>17 (27%)</td>
<td>5 (31%)</td>
<td>14 (36%)</td>
</tr>
<tr>
<td>Visited other professional health care giver (%)</td>
<td>18 (29%)</td>
<td>25 (40%)</td>
<td>3 (19%)</td>
<td>14 (36%)</td>
</tr>
<tr>
<td>Used anti-depressants, sedatives or sleeping pills (%)</td>
<td>20 (32%)</td>
<td>23 (37%)</td>
<td>7 (44%)</td>
<td>13 (33%)</td>
</tr>
</tbody>
</table>

*Differences within groups and between groups did not reach significance.*

**Participants with a diagnosis of PD versus those with no diagnosis**

Neither ITT nor completers-only analyses showed differences, on any outcome measure, between participants with and without clinical PD.
**Intervention adherence**

Of the 63 participants in the intervention group, 60 started lesson 1, while 3 participants did not log in at all (Figure 1). Almost half of the participants completed lesson 2. Five participants finished all 6 modules of DPO, 4 of them within the given 3-month time frame. During the trial, several participants reported that they experienced difficulties accessing the website. Those participants in the intervention group who completed T1 but did not complete the intervention (n = 30) were asked why they dropped out. The most frequently reported reasons involved time constraints (n = 13), life events (n = 5), and symptoms so severe that the individual was unable to follow the programme (or parts thereof) or carry out the assignments (n = 5; see Table 5).

**Table 5.** Reasons why participants did not finish Don’t Panic Online within 12 weeks. n = 30.

<table>
<thead>
<tr>
<th></th>
<th>n*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General issues</strong></td>
<td>30</td>
</tr>
<tr>
<td>Time constraint (too busy or need more time)</td>
<td>13</td>
</tr>
<tr>
<td>Life events (pregnancy, loss, family issues)</td>
<td>5</td>
</tr>
<tr>
<td>Symptoms too severe to do assignments</td>
<td>5</td>
</tr>
<tr>
<td>Found other therapy</td>
<td>4</td>
</tr>
<tr>
<td>Spontaneous recovery</td>
<td>2</td>
</tr>
<tr>
<td>Not motivated</td>
<td>1</td>
</tr>
<tr>
<td><strong>Issues related to the intervention</strong></td>
<td>7</td>
</tr>
<tr>
<td>Content not applicable</td>
<td>3</td>
</tr>
<tr>
<td>Adverse effect</td>
<td>1</td>
</tr>
<tr>
<td>More guidance needed</td>
<td>1</td>
</tr>
<tr>
<td>DPO lacks structure</td>
<td>1</td>
</tr>
<tr>
<td>Lessons too slow</td>
<td>1</td>
</tr>
</tbody>
</table>

*Numbers do not add up to 30, because 2 participants did not give reasons and others gave several.

**Discussion**

This study showed that the internet-based guided self-help intervention Don't Panic Online (DPO) was not effective in individuals with panic symptoms. Completers-only analyses did show moderate to large effect sizes between groups, in favour of the intervention group. Adherence to the treatment was low. An analysis of the data using a less conservative imputation method revealed significant effects between
groups in terms of the scores for general anxiety and depressive symptoms, but not for panic symptoms. Overall, the results show that DPO could be efficacious for intervention completers, but that it is not generally effective.

Comparisons with the literature
A meta-analysis revealed that, on average, the psychological treatment (offline and online) of full blown PD is highly effective, compared with a waiting-list control group, with a mean effect size of $d = 1.19$ (Sanchez-Meca, et al., 2010). Samples in which more than 50% of the participants had comorbid disorders did not benefit quite so much, but they still show a large effect size even when compared with pooled active and non-active control groups ($d = 0.83$) (Sanchez-Meca, et al., 2010). Self-help interventions have an average effect size of $d = 0.75$, again when compared with pooled control groups (Sanchez-Meca, et al., 2010). The results of our completers-only analyses are in line with these findings. Treatment adherence is not reported in this meta-analysis, only study drop-out rates, which averaged 9.53% for intervention groups.

In terms of study design and intervention, our study is comparable with the trial of Meulenbeek et al. (Meulenbeek, et al., 2010). That study found a moderate effect size of $d = 0.68$ for the face-to-face group course Don’t Panic, an intervention whose content is quite similar to DPO. Treatment completion, defined as having followed at least six of the eight sessions, was 75%. In that study, the participants had a relatively low baseline mean PDSS-SR score (7.2), which is similar to our study’s findings. Aside from panic symptoms, however, the sample differed from ours in a number of ways. Meulenbeek et al. excluded participants with severe disorders other than PD, as well as those with social problems, and those who were receiving treatment for panic symptoms. In general, group interventions are no more effective than guided self-help interventions (Cuijpers, Donker, Van Straten, Li, & Andersson, 2010). Possibly, any differences in outcome between the trials of Don’t Panic and Don’t Panic Online might be attributed to inclusion criteria.

Previous studies that compared internet-based guided self-help for panic symptoms with a control group showed an overall effect size of Hedge’s $g = 0.83$ (Andrews, et al., 2010). Like DPO, the interventions studied were based on cognitive behavioural therapy and were similar in length (Carlbring, et al., 2006; Klein, et al., 2006; Wims, et al., 2010). Compared with these studies, effect sizes in the current study were expected a priori to be lower. We included a less severe group, thereby ruling out large decreases in symptom severity. Accordingly, assuming that there was no deterioration in the control group, the difference between the intervention group and control group at T1 could not be as large. With
regard to low treatment adherence, this was not found in previous studies and values range from 79% to 95% (Andrews, et al., 2010; Klein, et al., 2006).

There are several differences between our study and previous studies that may have had an impact on adherence. Firstly, all participants in our trial were free to use medication and find other treatment. Some may have found other help and decided to quit DPO. Secondly, our participants reported technical difficulties. Thirdly, previous researchers had more telephone contact with their participants (Carlbring, et al., 2006; Klein, et al., 2006). Our participants were also not interviewed after the treatment, while a scheduled interview after treatment may lead to better adherence (Nordin, Carlbring, Cuijpers, & Andersson, 2010). Fourthly, the intervention we studied was not the same as the interventions of other studies. Perhaps DPO is not as effective or attractive as those examined in other studies. Lastly, our sample included a large proportion of participants with comorbid disorders, and possibly a proportion of participants who did not have PD as primary diagnosis. Perhaps an internet-based intervention specifically for panic symptoms is less suited to this group. However, epidemiological data show that panic symptoms often coincide with psychiatric disorders other than PD (Batelaan, De Graaf, et al., 2007; Bystritsky, et al., 2010). Therefore, the participants of our study appear to be a representative sample of individuals with panic symptoms.

In summary, both clinical effect and treatment adherence were lower in our study than in previous studies of internet-based self-help interventions and the Don’t Panic group course. The differences in sample characteristics between our study and previous trials could indicate that internet-based interventions for panic symptoms are efficacious but that, in general, they may not be effective for all individuals seeking help for panic symptoms.

Limitations
When interpreting our results, several limitations should be taken into account. One limitation of this study is non-response at the post-treatment measurement. For a large proportion of participants, it is unknown whether their panic symptoms increased, decreased, or remained stable. These missing values were estimated by multiple imputation. While this can be considered a conservative imputation method, it is unlikely that the imputed values greatly underestimate the intervention effect. This is because many of the participants who did not respond to T1 also left the intervention after one or two sessions, and are therefore unlikely to have gained much benefit from it. A second limitation is that the intervention completers are small in number and may not be representative of the intervention group as a whole, even though there did not appear to be significant differences between
completers and non-completers. The comparison of this select group with the control group, for completers-only analyses, should be interpreted with caution. Thirdly, the control group could have had gained some benefit from the information website, which could have decreased the difference between T1 mean scores of the intervention group and control group. If that is the case, our study proved that DPO has, in general, no added value compared with an information website and our conclusion would remain the same. A fourth limitation is the lack of a follow-up measurement. It is not known whether the participants in either the intervention group or the control group showed any further improvement over the subsequent months to a year. Finally, all continuous measures were obtained by online self-report. The PDSS-SR could potentially yield lower mean scores than the PDSS interview (Wuyek, et al., 2011), while online versions of questionnaires could potentially yield higher mean scores than pencil-and-paper versions (Cuijpers, Boluijt, & Van Straten, 2008; Donker, Van Straten, Marks, & Cuijpers, 2011). These differences in psychometric properties limit the comparison of this study with other studies. However, this imposes no restrictions on comparisons between the intervention group and control group within our own study and, additionally, online and pencil-and-paper versions of panic questionnaires do appear to be equivalent (Austin, Carlbring, Richards, & Andersson, 2006; Carlbring, et al., 2007).

**Implications and future research**

As our study and others have shown, panic symptoms generally coincide with comorbid symptoms. Internet-based transdiagnostic self-help programmes, tailored to the anxiety and/or depressive symptoms of the participant, show promising results in terms of the treatment of panic and other common mental disorders (Carlbring, et al., 2011; Silfvernagel, et al., 2012; Titov, Andrews, Johnston, Robinson, & Spence, 2010). Tailored interventions could be more effective for individuals with higher symptom severity and comorbidity rates than non-tailored programmes (Johansson, et al., 2012). Tailoring might help to increase treatment adherence, as participants would then only see those sections that are applicable to them. Given the results of our study, the further development of transdiagnostic and tailorable internet interventions should be encouraged.

Future research could focus on identifying those groups for whom internet-based self-help interventions are effective, by means of predictor and mediator analyses, for example. Further research is also needed to investigate ways of boosting treatment adherence to DPO, of making it a feasible intervention for mild to moderate panic symptoms, and perhaps of modifying it to become more
tailorable and transdiagnostic in nature. This was the first study of internet-based
guided self-help for mild panic symptoms and our study needs to be replicated
before we can draw any definitive conclusions. Lastly, while the efficacy of
internet-based guided self-help interventions has been established in several
studies, it should be encouraged to conduct more pragmatic RCTs to examine the
effectiveness.

References

anxiety and depressive disorders is effective, acceptable and practical health care: a meta-

commonly used questionnaires in panic research: equivalence to paper administration in
Australian and Swedish samples of people with panic disorder. International Journal of

health and thresholds for illness: panic disorder versus subthreshold panic disorder. Psychol

127-136.


subthreshold panic disorder. Depress Anxiety, 27(4), 381-389.

treatment of panic disorder: a randomized trial of internet-based cognitive behavior therapy

paper and pencil administration of questionnaires commonly used in panic/agoraphobia


Lawrence Erlbaum Associates.

Internet: sensitivity and specificity of two screening questionnaires. European Child &
Adolescent Psychiatry, 7, 32-38.

effective as face-to-face psychotherapy for depression and anxiety disorders? A systematic
review and meta-analysis of comparative outcome studies. Psychol Med, 40(12), 1943-
1957.


