Chapter 1

General introduction
Introduction

The main aim of this thesis is to evaluate the effectiveness and feasibility of an early intervention for panic symptomatology in its natural setting. The intervention is called the ‘Don’t Panic’ course and is based on cognitive behavioural principles.

This introductory chapter addresses the nature, aetiology and maintaining factors of panic attacks and panic disorder, considers the epidemiology of anxiety disorders, and zooms in on prevention of anxiety disorders. The introduction ends with an overview of the main research questions and an outline of the studies described in each of the remaining chapters of this thesis.

Panic symptoms, its nature, aetiology and maintaining factors

Although feelings of fear in dangerous situations are normal and can be life-saving, these feelings can be debilitating when they occur in situations that are not dangerous. The latter may take the form of panic attacks. Panic attacks can be terrifying experiences. They can be characterised as discrete episodes of intense fear or discomfort in the absence of real danger, accompanied by four (or more) of the following symptoms (1) palpitations or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) dizziness, unsteady feelings, or faintness; (9) derealization or depersonalization; (10) fear of going crazy or doing something uncontrolled; (11) fear of dying; (12) tingling or numbness; and (13) chills or hot flushes. The symptoms develop abruptly, reach a peak within 10 minutes and typically last for about 30 minutes. People suffering from panic attacks may be at risk of developing panic disorder. Panic disorder is defined by recurrent unexpected panic attacks, followed by at least a month of persistent concern about having additional attacks, worry about possible implications of the attack or its consequences (e.g., losing control, having a heart attack), or a significant change in behaviour related to the attacks (e.g., avoiding situations associated with attacks, undergoing frequent medical check-ups). Furthermore, the panic attacks should not be the direct result of a substance (e.g., a drug) or a general medical condition (e.g., hyperthyroidism), and are not better accounted for by another mental disorder (e.g., social phobia, specific phobia).

There are many models on the aetiology of PD other than cognitive behavioural models (e.g., biological models, psychodynamic models). Because the intervention described in this thesis is based on cognitive behavioural therapy, only the two dominating and complementary cognitive behavioural models will be reported. A major model of the aetiology of panic disorder is described by Barlow. According to this biopsychosocial model, a generalized biological (heritable) vulnerability may cause a heightened stress-response arousal. This vulnerability may become activated by early psychological experiences of uncontrollability and unpredictability (i.e., generalized psychological vulnerability). In stressful situations these two vulnerabilities may lead to the development of a specific psychological vulnerability (i.e.,
the conviction that unexplained physical sensations are dangerous), which in turn may lead to anxious apprehension (i.e., heightened focus on somatic sensations) and eventually PD. Another major model is the cognitive model described by Clark\(^3\).

![Image](image_url)

**Figure 1.** Clark’s cognitive model of panic\(^3\)

This model was developed to explain the process by which panic attacks occur. According to this model, panic attacks are the result of the catastrophic misinterpretation of certain benign arousal-related bodily sensations (e.g., pounding heart, dizziness). The catastrophic misinterpretation (i.e., the misinterpretation of these sensations as more dangerous than they really are; e.g., as signs of impending insanity, loss of control, or death) leads the person to become further alarmed, and convinced of a forthcoming disaster. This feeds the anxiety and increases the intensity of the anxious sensations, and so on, in a vicious cycle ending in a panic attack. Through the processes of selective attention and avoidance and safety behaviours this tendency to misinterpret certain benign arousal-related bodily sensations in a catastrophic way continues to exist.

**Epidemiology of anxiety disorders**

Epidemiological studies on the prevalence of anxiety disorders in the general population have revealed high levels of these types of psychopathology. Anxiety disorders appear to be the most common psychiatric disorders worldwide. The National Comorbidity Survey Replication (NCS-R) in the United States\(^4,5\) revealed a lifetime prevalence rate of anxiety disorders in the adult population of 29%. The 12-month prevalence of an anxiety disorder was 18%. In the Netherlands Mental Health Survey and Incidence Study (NEMESIS) the lifetime prevalence rate of anxiety disorders was 19.3%, and the 12-month rate was 12.4% based on DSM-III-R criteria\(^6\). For panic disorder the NEMESIS study revealed a lifetime prevalence rate of 3.8%
and a 12-month rate of 2.2%. Furthermore, the NEMESIS data showed that the incidence of panic disorder is high, relative to its prevalence: about 35% of all cases of PD each year are new. A literature search showed that the 12-month prevalence of DSM-III-R panic disorder of the reviewed epidemiological surveys in the European Union clustered around 2%. A large population segment suffers from panic attacks and may be at risk of developing full-blown panic disorder. An epidemiological survey based on DSM IV criteria by Kessler et al. estimated that lifetime prevalence of isolated panic attacks without agoraphobia (PA Only) occurred in 22.7% of the adult population in the United States. For panic attacks with agoraphobia (PA-AG) the percentage was 0.8%, for panic disorder (PD) without agoraphobia (PD Only) 3.7%, and for panic disorder with agoraphobia (PD-AG) 1.1%. The estimated 12-month prevalence rates were: PA Only 11.2%, PA-AG 0.4%, PD Only 2.8% and PD-AG 0.4%. Furthermore, the survey showed that all panic subgroups show meaningful role impairments and high comorbidity with other psychiatric disorders (e.g., other anxiety disorders, mood disorders). A study by Batelaan et al. examined a large representative sample of the general adult population of the Netherlands (N = 7,076) and concluded that subthreshold panic disorder seems clinically relevant, occupying an intermediate position between panic disorder and no-panic. The economic costs of anxiety disorders are extensive and comparable to those of somatic disorders. In addition, panic disorder was associated with the largest costs of all anxiety disorders in the study by Smit et al. Another study on the economic costs of panic disorder showed that the annual per capita costs of subthreshold panic disorder and of panic disorder were substantial (€6,384 vs. €10,269). The prevalence of panic disorder among women appears to be twice as large as among men. Furthermore, the median age of onset is 24.

**Prevention of anxiety disorders**

The public health importance of prevention of anxiety disorders is emphasized by its high prevalence, early onset, large burden of disease, and considerable economic costs to society. Furthermore, only a minority of the people with an anxiety disorder receive empirically supported treatments and even if they all received the best possible treatment, the proportion of burden averted would still be low.

According to the Institute of Medicine (IOM) prevention programmes can be divided into three categories: universal, selective, or indicated. Universal prevention programmes target a whole population or all members of a specific group (schoolchildren, adolescents, adults) without regard for risk factors. An example of such a prevention program is an intervention using cognitive-behavioural techniques (i.e., FRIENDS = acronym for Feeling worried; Relax and feel good; Inner helpful thoughts; Explore plans; Nice work; Don’t forget to practice; and Stay calm for life) for children in primary school settings. Selective prevention aims at persons at risk for a disorder. For example Smidt et al. used anxiety sensitivity as a risk factor in the pathogenesis of anxiety disorders and examined the effect of a brief intervention...
(ASAT = Anxiety Sensitivity Amelioration Training) to decrease anxiety sensitivity. Indicated prevention targets persons who show subthreshold symptoms of an anxiety disorder. Dadds et al.\textsuperscript{20} examined one of the first examples of indicated prevention for children with subthreshold or mild anxiety disorder (QEIPAP = the Queensland Early Intervention and Prevention of Anxiety Project).

Despite the public health importance of prevention of anxiety disorders, studies on the effectiveness of prevention programmes are rare\textsuperscript{21,22}. Apart from simple education and prescribing medication, most prevention programmes have been based on cognitive-behavioural principles. Initial evaluations suggest that the results of preventive interventions based on cognitive and behavioural principles are promising.

Only a few studies have been conducted in prevention and early intervention (i.e., intervention for people with mild PD) for panic symptoms in adults. Whereas prevention targets persons without a disorder, early intervention target persons who meet criteria for a disorder but are in the less severe range. Gardenswartz and Craske\textsuperscript{23} studied an indicated preventive intervention. They tested a 1-day panic prevention program for students with subthreshold PD. Findings indicated that by 6-month follow-up nine (13.6\%) of the 66 participants who were randomly assigned to the wait-list control group developed panic disorder in contrast with only one (1.8\%) of the 55 participants in the intervention group. A study by Swinson, Soulis, Cox, and Kuch\textsuperscript{24} looked at the impact of a brief early intervention for adults with panic attacks seen in an emergency medical setting. They used a structured clinical interview and found that approximately 40\% met the criteria of PD with agoraphobia. The 33 participants were randomly assigned to groups receiving reassurance (n = 16) or exposure instruction (n = 17). Over 6-months’ follow-up, the exposure group significantly improved in symptoms of panic frequency, avoidance and depression, whereas the reassurance-only group did not improve on any of these variables. The results of these studies suggest that prevention and early intervention for panic symptoms is a promising option. However, these studies lack generalizability, given the use of a limited sample (i.e., college students; and patients with panic attacks seen in an emergency room).

We developed a preventive intervention for adults with panic symptoms. The intervention is based on cognitive behavioural principles and aims at reducing panic symptomatology. The intervention is called the ‘Don’t Panic’ course and its effectiveness and feasibility will be studied in this thesis. To strengthen external validity of the present study, the ‘Don’t Panic’ course was studied in its natural setting. To that end, both the recruitment strategy and the way the intervention was delivered are congruent with operational modes that are employed by the community mental health centres in the Netherlands. The ‘Don’t Panic’ course can be categorized as an indicated prevention program as far as it targets people with subthreshold panic disorder; it can be categorized as an early intervention program as far as it is aimed at people with a panic disorder who are in the less severe range.
Although there are some studies indicating that subthreshold and mild forms of psychopathology may have a significant impact on a person's life\textsuperscript{25,26}, little is known about the impact different degrees of severity in subthreshold and mild panic disorder can have on levels of personal and social functioning as well as on economic costs. A considerable impact on level of functioning and economic costs for different degrees of panic severity makes intervening more justifiable. Furthermore, when an intervention appears to be equally effective in various less severe panic subgroups it could be implemented broadly as a first step in a stepped care approach to mental health. Therefore, this thesis also compares levels of severity in subthreshold and mild panic disorder on sociodemographic characteristics, clinical and economic variables, and on improvement after the ‘Don’t Panic’ course. There is a lack of knowledge of how and why interventions produce change. Research into the process of change underlying clinical improvement of interventions is scarce. Knowledge about the process of change may help to increase the efficacy of the intervention. Therefore, this thesis addresses the process of change underlying clinical improvement.

Outline of the thesis

Panic disorder is a common mental disorder and the incidence of panic disorder is high. It is associated with a large burden of disease, considerable medical consumption and extensive economic costs. Prevention and early intervention in PD are therefore of public interest, and a panic prevention and early intervention program delivered to subjects with subthreshold or mild PD may decrease current panic disorder symptomatology. Studies that have been conducted in early intervention for panic symptoms in adults are scarce and lack generalizability. This study was designed to examine the effectiveness and feasibility of a preventive and early intervention for panic symptomatology in its natural setting to strengthen the external validity.

This thesis will examine the following research questions:
1. Is a short version of the ‘Don’t Panic’ course equally as effective as the long version?
2. Is the course effective and feasible?
3. Do varying degrees of panic severity differ in impact on level of functioning and intervention outcome?
4. What is the process of change underlying improvement?

The second chapter deals with the first and second research questions. It examines the effects and feasibility of the ‘Don’t Panic’ course in a sample of 114 self-referred people suffering from panic attacks in an uncontrolled pilot study. In addition, the effectiveness of two modifications of the course (8 vs. 12 sessions) is compared. The results of this study are used to make a ‘best practice’ version of the ‘Don’t Panic’ course.

In the third chapter, a study protocol is described to examine the (cost-) effectiveness of the ‘best practice’ version of the ‘Don’t Panic’ course in a sample of self-referred people presenting with subthreshold or mild PD in a randomised controlled trial.
The fourth chapter discusses the second research question. It presents the results of randomised controlled trial on the effectiveness of the intervention, offered by community mental health centres, in a sample of 217 self-referred people presenting with subthreshold or mild PD.

The fifth chapter addresses the third research question using data of the randomised controlled trial. It describes a study comparing degrees of severity in subthreshold and mild panic disorder on sociodemographic characteristics, on levels of psychological and social functioning and on economic costs. Furthermore, differences in improvement after the intervention were examined. If all degrees of severity in panic are associated with a large burden of disease, incur considerable costs to society, and may benefit from an early intervention for panic, this would have implications for general clinical practice, because it would show that an early intervention for less severe panic could be implemented broadly as a first step in a stepped-care mental health approach.

The sixth chapter focuses on the fourth research question using data of the randomised controlled trial. It considers the process of change underlying improvement after the intervention, by presenting the results of a study on cognitive mediation during the intervention. Knowledge about the process of change may increase the efficacy of the intervention.

In the final chapter, the major findings of the studies presented are summarised and discussed. The scientific and public health relevance of the study is discussed, followed by directions for the future.
REFERENCES

Chapter 2

Effects and feasibility of a preventive intervention in sub-threshold and mild panic disorder: results of a pilot study

ABSTRACT

Background
Panic disorder (PD) is a serious DSM-IV axis I disorder affecting up to 3% of the adult population each year. It is associated with a large burden of disease and extensive economic costs. This study aims to examine the effects and feasibility of the ‘Don’t Panic’ course, a preventive cognitive behavioural intervention in sub-threshold and mild PD. It also compares the effectiveness of two modifications of the course (8 vs. 12 sessions).

Methods
The method used was a quasi-experimental two-group pre-post design with a baseline measurement (T0) and two follow-up measurements. Follow-ups were at the end of the intervention (T1) and six months later (T2). Primary outcome measure was the Panic Disorder Severity Scale-Self Report. A total of 114 participants suffering from panic attacks (mean age 42 years; 78% female) entered the study.

Results
The course participants showed a significant effect on the outcome measures at follow-up. Large effect sizes were found on panic symptoms, on symptoms of agoraphobia and on mental health-related quality of life at T1 and T2. Overall, the course leaders and the participants evaluated the course positively. There were no significant differences in outcome measures between the short and the long version of the course.

Conclusions
The study suggests that people with sub-threshold PD and mild PD could benefit from this preventive intervention and that the intervention might be feasible. Furthermore, the short version could be as effective as the long version.
BACKGROUND

Panic disorder (PD), affecting 2% to 3% of the adult population each year\(^1,2\), is associated with a large burden of disease, considerable medical consumption and extensive loss of productivity\(^3,4\). The incidence of PD is high (about 35% of all cases each year of PD are new\(^1\)), indicating the importance of prevention and early intervention in PD.

A substantial proportion of the population suffers from sub-threshold PD\(^5,6\). Sub-threshold PD can be defined as the presence of some symptoms of PD, not meeting the DSM-IV diagnostic criteria. These subjects may be at risk of developing full-blown PD\(^7\).

Studies on prevention and early intervention in anxiety disorders indicate that prevention of anxiety disorders through cognitive-behavioural interventions can be successful\(^8,9\). Only a few studies have been conducted on the prevention of panic disorder\(^10,11\). The results of these studies suggest that prevention of panic disorder is a promising option.

As a pilot project we developed a preventive intervention for adults with panic symptoms, called the ‘Don’t Panic’ course. The course is based on cognitive-behavioural principles and makes use of interventions that have appeared effective in the treatment of PD before\(^12,13\).

The aim of this study was to examine the effects and feasibility of the ‘Don’t Panic’ course in a sample of self-referred people suffering from panic attacks in an uncontrolled pilot study. In addition, the effectiveness of two modifications of the course (8 vs. 12 sessions) was compared.

METHODS

Research design

We used a quasi-experimental two-group pre-post design with a baseline measurement (T0), a post-test measurement at the end of the course (T1) and a follow-up measurement, 6 months after the course (T2). The study was designed to mimic the Dutch health care system as naturalistically as possible in terms of participant recruitment and the manner in which intake, offering the intervention, and monitoring outcomes are conducted. Because the study simulates the usual practice in the Netherlands, an ethical approval was not necessary.

Participants

Participants were recruited from the general population through advertisements in regional newspapers and information brochures at general practices. For screening, the standard procedures employed by the Community Mental Health Centres were used. Firstly, interested persons were given more information about the course and underwent initial screening by telephone to ascertain the presence of panic symptoms. Secondly, potential participants had a face-to-face clinical interview with a clinician (i.e., experienced psychologist) from a Community Mental Health Centre. The clinician used a list with inclusion and exclusion
criteria. Depending on the impression formed by the clinicians, potential participants were included or excluded. Those included in the study were people with sub-threshold panic disorder or mild panic disorder with or without additional agoraphobic problems (i.e., low degree of symptom severity and little interference in work or social functioning). Exclusion criteria were severe PD (i.e., high degree of symptom severity and substantial interference in work or social functioning), other current psychiatric diagnoses or suicidality warranting treatment or likely to interfere with participation in the group course. People meeting one of the exclusion criteria were advised to seek regular treatment. If a participant used medication for anxiety or depression (e.g., anxiolytics or antidepressants), it was agreed not to change the medication while attending the course. The participants were receiving no other form of psychotherapy.

For the participants’ flow through the study see Figure 1. To join the study, the participant had to sign a written informed consent. Fifty-four participants refused to take part in the research (32%; mainly because they didn’t feel like it), but were allowed to attend the course. A total of 114 participants were enrolled in the study and completed the baseline measurements. In Table 1, the characteristics of the course participants are presented.

A comparison of demographic and clinical status variables of the participants at baseline (T0) between the short (N=36) and the long (N=78) version of the course demonstrated no significant differences.

**Figure 1.** Participants’ flow through the study

*Note.* PD = Panic Disorder.
### Table 1.
Characteristics of the course participants for Total Group, Short Version and Long Version

<table>
<thead>
<tr>
<th></th>
<th>Total group (N=114)</th>
<th>Long version (N=78)</th>
<th>Short version (N=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, N (%)</td>
<td>89 (78.1)</td>
<td>64 (82.1)</td>
<td>25 (69.4)</td>
</tr>
<tr>
<td>Mean age, Years (SD)</td>
<td>41.7 (11.4)</td>
<td>42.4 (11.4)</td>
<td>40.3 (11.5)</td>
</tr>
<tr>
<td>Married/living with partner, N (%)</td>
<td>87 (76.3)</td>
<td>58 (74.3)</td>
<td>29 (80.6)</td>
</tr>
<tr>
<td>Employed (paid), N (%)</td>
<td>85 (74.6)</td>
<td>56 (71.8)</td>
<td>29 (80.6)</td>
</tr>
<tr>
<td>Educational level, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>22 (19.3)</td>
<td>15 (19.2)</td>
<td>7 (19.4)</td>
</tr>
<tr>
<td>Middle</td>
<td>51 (44.7)</td>
<td>36 (46.2)</td>
<td>15 (41.7)</td>
</tr>
<tr>
<td>High</td>
<td>41 (36.0)</td>
<td>27 (34.6)</td>
<td>14 (38.9)</td>
</tr>
<tr>
<td>More than 1 year of panic symptoms, N (%)</td>
<td>95 (83.3)</td>
<td>65 (83.3)</td>
<td>30 (83.3)</td>
</tr>
<tr>
<td>Medication for anxiety or depression, N (%)</td>
<td>64 (56.1)</td>
<td>42 (53.8)</td>
<td>22 (61.1)</td>
</tr>
<tr>
<td>SCL-90 Anx, M (SD) (range: 0-4)</td>
<td>1.26 (0.72)</td>
<td>1.31 (0.76)</td>
<td>1.15 (0.63)</td>
</tr>
<tr>
<td>SCL-90 Pho, M (SD) (range: 0-4)</td>
<td>1.13 (0.83)</td>
<td>1.16 (0.84)</td>
<td>1.09 (0.81)</td>
</tr>
<tr>
<td>SCL-90 Dep, M (SD) (range: 0-4)</td>
<td>0.89 (0.62)</td>
<td>0.89 (0.63)</td>
<td>0.88 (0.61)</td>
</tr>
<tr>
<td>PDSS-SR, M (SD)* (range: 0-28)</td>
<td>8.7 (5.0)</td>
<td>8.8 (5.5)</td>
<td>8.6 (4.1)</td>
</tr>
<tr>
<td>Subclinical (score 0-7), N (%)</td>
<td>36 (40.4)</td>
<td>25 (47.2)</td>
<td>11 (30.6)</td>
</tr>
<tr>
<td>Clinical (score 8-28), N (%)</td>
<td>53 (59.6)</td>
<td>28 (52.8)</td>
<td>25 (69.4)</td>
</tr>
</tbody>
</table>

*Note. SCL-90 = Symptom Check-List: Anx = anxiety, Pho = phobic anxiety, Dep = depression; PDSS-SR = Panic Disorder Severity Scale-Self Report. * based on n=89 (the PDSS-SR was not used on the first 3 courses).

### Measures

Primary outcome measure for panic and agoraphobic symptoms was the self-report version of the Panic Disorder Severity Scale\textsuperscript{14}. The Panic Disorder Severity Scale-Self Report (PDSS-SR) has good psychometric properties (Cronbach’s alpha=0.92; intraclass correlation coefficient=0.81)\textsuperscript{15}. Secondary outcomes for panic symptoms consisted of the Body Sensation Questionnaire (BSQ1)\textsuperscript{16} and the subscale anxiety of the Symptom Check-List (SCL-90)\textsuperscript{17}.  

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For symptoms of agoraphobia the secondary outcomes were the Agoraphobic Cognitions Questionnaire (ACQ)\textsuperscript{16} and the Mobility Inventory (MI)\textsuperscript{18}. In addition, the subscale phobic anxiety of the SCL-90\textsuperscript{17} was used. For mental health-related quality of life, the outcome measure was the subscale mental health of the MOS Short-Form General Health Survey (MOS-SF-20 Mh)\textsuperscript{19}. To measure general symptoms of depression, the subscale depression of the SCL-90\textsuperscript{17} was used. Moreover, the Mastery-scale\textsuperscript{20} was used to assess locus of control. All scales have good psychometric properties\textsuperscript{16-20}. Only on the MOS-SF-20 MH and the Mastery-scale does a higher rating indicate a more favourable outcome.

**Intervention**

The ‘Don’t Panic’ course includes a course manual\textsuperscript{21}, to be used by the clinician and prevention specialist offering the intervention, as well as a participant workbook\textsuperscript{22}. The course involves (a) psycho-education about the nature and physiology of anxiety and panic attacks, (b) changing life-style to enhance physical condition, (c) stress management to prevent constant stress by learning effective ways to cope with stressors, (d) relaxation training to reduce physiological arousal, (e) cognitive restructuring to challenge and correct faulty beliefs regarding panic and anxiety, (f) interoceptive exposure to reduce the fear of somatic sensations, and (g) ‘in vivo’ exposure to reduce avoidance of situations and use of safety behaviours. Furthermore, techniques aimed at relapse prevention are taught. The short course consists of 8 weekly, two-hour group sessions; the long version contains 12 weekly, two-hour group sessions of 6 to 12 participants. Both versions have the same elements. The long version has more sessions containing ‘in vivo’ exposure.

**Procedure**

Clinicians and prevention specialists from 12 community mental health centres were trained in the selection procedure of participants (e.g., using the inclusion and exclusion criteria) and in using the course manual to conduct the course. Integrity of intervention delivery was maintained by utilizing a structured and manual-based course protocol.

The twelve-session course was run by 9 centres and the 8 session course by 6 centres (3 centres offered both versions of the course; one mental health centre offered the long version of the course four times. In these cases the time between two courses was about two months and a person participated in the course offered at the time the person entered the study. There was no selection of participants to the two versions of the course.). In total, the data contains the results of 18 courses.

Data collection was conducted by an independent research institute. Assessments consisted solely of self-report measures through postal questionnaires and were completed at home.
Statistical analyses
Analyses were conducted on an intention-to-treat basis. The effect of the intervention was analysed with a Repeated Measures ANOVA, Simple Contrast. Effect sizes (d) were obtained by subtracting post-test (T1) or follow-up (T2) means from baseline (T0) means and then dividing the difference by the pooled standard deviation. The categorization of Lipsey and Wilson\textsuperscript{23} was used for clinical interpretations of the d's.

The difference between the short and the long version of the course on the severity of panic symptoms was analysed with a 2 Group (8 vs. 12 sessions) x 3 Time (baseline, post-test, 6 month follow-up) Repeated Measures ANOVA, with Group as the between-subject factor and Time as within-subject factor. Levels of severity of panic symptoms (PDSS-SR) constituted the dependent variable. Wilks' lambda (\(\lambda\)) was used as multivariate criterion for significance. The same analysis was performed on all the other outcome measurements.

The significance level was set at \(\alpha = 0.05\), two-sided.

RESULTS

Outcome
Table 2 presents an overview of the results on the measurements. The course participants showed a significant effect on the primary outcome measure and secondary outcome measures at post-test and follow-up. Large effect sizes were found on panic symptoms and on symptoms of agoraphobia at T1 and T2. In addition, large effect sizes were found on mental health-related quality of life at T1 and T2 and on depression at T2. The increase of internal locus of control after the intervention showed medium effect sizes. Effects remained stable from post-test to follow-up.

The Repeated Measures ANOVAs on the outcome measures showed a significant effect of time, no significant group effect between the short and the long version of the course and no significant interaction effect for time x group (Table 3).

Medication use at baseline had no significant impact on the residualized change scores at T1 on the primary outcome measure (PDSS-SR; point-biserial correlation; \(r=0.12, p=0.249\)). For the other outcome measures at T1 (except for MOS-SF-20Mh; point-biserial correlation; \(r=-0.20, p=0.029\)) and for all outcome measures at T2, the results of the analyses were comparable.
Table 2.
Means, Standard Deviations, Repeated Measures ANOVA, Simple Contrast and (range) Effect Sizes (d) for Baseline (T0), Post-test (T1), and Follow-up (T2) (N=114)

<table>
<thead>
<tr>
<th>Scale measure</th>
<th>T0 Mean (SD)</th>
<th>T1 Mean (SD)</th>
<th>T2 Mean (SD)</th>
<th>T0-T1 Size (d)</th>
<th>Range (d)</th>
<th>T0-T2 Size (d)</th>
<th>Range (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDSS-SR* (range: 0-28)</td>
<td>8.74 (4.98)</td>
<td>5.03** (4.98)</td>
<td>5.07** (5.39)</td>
<td>0.75</td>
<td>-1.9–2.8</td>
<td>0.71</td>
<td>-3.1–3.2</td>
</tr>
<tr>
<td>BSQ1 (range: 1-5)</td>
<td>2.04 (0.62)</td>
<td>1.47** (0.49)</td>
<td>1.42** (0.60)</td>
<td>1.02</td>
<td>-1.0–5.3</td>
<td>1.02</td>
<td>-1.7–3.6</td>
</tr>
<tr>
<td>ACQ (range: 1-5)</td>
<td>2.00 (0.66)</td>
<td>1.47** (0.60)</td>
<td>1.42** (0.56)</td>
<td>0.84</td>
<td>-0.8–3.6</td>
<td>0.95</td>
<td>-1.5–3.1</td>
</tr>
<tr>
<td>MI (range: 1-5)</td>
<td>2.15 (0.78)</td>
<td>1.65** (0.73)</td>
<td>1.61** (0.60)</td>
<td>0.66</td>
<td>-1.6–3.5</td>
<td>0.77</td>
<td>-2.8–3.5</td>
</tr>
<tr>
<td>SCL-90 Anx (range: 0-4)</td>
<td>1.26 (0.72)</td>
<td>0.68** (0.64)</td>
<td>0.62** (0.60)</td>
<td>0.84</td>
<td>-1.1–4.4</td>
<td>0.96</td>
<td>-2.1–4.4</td>
</tr>
<tr>
<td>SCL-90 Pho (range: 0-4)</td>
<td>1.13 (0.83)</td>
<td>0.63** (0.72)</td>
<td>0.50** (0.60)</td>
<td>0.64</td>
<td>-1.7–3.9</td>
<td>0.88</td>
<td>-2.1–3.9</td>
</tr>
<tr>
<td>SCL-90 Dep (range: 0-4)</td>
<td>0.89 (0.62)</td>
<td>0.56** (0.59)</td>
<td>0.51** (0.57)</td>
<td>0.55</td>
<td>-1.2–3.2</td>
<td>0.63</td>
<td>-3.8–3.4</td>
</tr>
<tr>
<td>MOS-SF-20 Mh (range: 0-100)</td>
<td>57.60 (16.43)</td>
<td>67.95** (17.09)</td>
<td>68.76** (18.38)</td>
<td>0.62</td>
<td>-1.7–2.7</td>
<td>0.64</td>
<td>-1.5–2.9</td>
</tr>
<tr>
<td>MASTERY* (range: 5-25)</td>
<td>17.47 (4.21)</td>
<td>18.91** (3.93)</td>
<td>19.11** (4.32)</td>
<td>0.35</td>
<td>-1.6–3.1</td>
<td>0.38</td>
<td>-1.8–2.7</td>
</tr>
</tbody>
</table>

Note. PDSS-SR = Panic Disorder Severity Scale-Self Report; BSQ1 = Body Sensation Questionnaire; ACQ = Agoraphobic Cognitions Questionnaire, total score; MI = Mobility Inventory, total score; SCL-90 = Symptom Check-List: Anx = anxiety; Pho = phobic anxiety; Dep. = depression; MOS-SF-20 = Medical Outcomes Study Short-Form General Health Survey (SF-20): Mh = mental health.
* based on n=89 (the PDSS-SR and MASTERY were not used on the first 3 courses).
** Repeated Measures ANOVA, Simple Contrast p < 0.001.
**Effects and feasibility of a preventive intervention**

*Feasibility and acceptability*

After each session the prevention specialists registered all the participants attending, and ascertained whether they had done their homework. On the basis of this information, the dropout rate (participants who indicated stopping the course, mainly because of work obligations or illness) was 13%; the mean number of attended sessions for the short version was 6.4 sessions (80%) and for the long version 9.0 sessions (75%). Of the participants attending a session, on average 91% had completed their homework. Therefore, compliance with the intervention was satisfactory.

The participants evaluated the course positively (organizational aspects, coaching, content, group sessions, and workbook). Asked whether the course had contributed to being more able to manage anxiety, 98% answered in the affirmative. Of the participants, 92% were “satisfied” or “very satisfied” with the course.

Overall, the course leaders also evaluated the course positively (content, time schedule, didactic elements). These findings suggest the intervention is feasible and acceptable.

**DISCUSSION**

In this study, the participants in the preventive course ‘Don’t Panic’ showed a significant reduction in panic and agoraphobic symptoms after the course. Large effect sizes were achieved in reducing panic and agoraphobic symptoms. The improvement was maintained over 6 months after the intervention. The results suggest that the course is acceptable and feasible. These findings converge with the findings of earlier research on the prevention of panic disorder\textsuperscript{10,11}.

Furthermore, symptoms of depression declined, as measured by the SCL-90. In addition, the internal locus of control and the quality of life increased significantly. These findings are important because people with panic symptoms may also have higher rates of other psychiatric symptoms\textsuperscript{24}.

We did not find any significant differences in outcome measures between the short and the long version of the course. A lack of power may play a role in this finding.

There are several limitations to the present study. Firstly, it lacked a structured psychiatric interview. Therefore, it is unclear how many participants might have been diagnosed with panic disorder or other psychiatric disorders at baseline, post-test and follow-up. Furthermore, the diagnosis of agoraphobia might have clarified whether it had an impact on the results. Secondly, 56% of the participants used medication for anxiety or depression at baseline. Although medication use at baseline did not predict outcome, continued use of medication may have hampered the effect of the intervention. This is because medication may have been used as a safety behaviour. Likewise, discontinuation of medication after psychological treatment may also have reduced treatment efficacy because patients may attribute the symptom reduction achieved to the use of medication and may lack self-confidence in being able to
Table 3.
Repeated Measures ANOVA on the outcome measures by group (N=114)

<table>
<thead>
<tr>
<th>Scale measure</th>
<th>Intervention (time) effect</th>
<th>Group (condition) effect</th>
<th>Interaction effect for intervention x group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F and p</td>
<td>F and p</td>
<td>F and p</td>
</tr>
<tr>
<td>PDSS-SR*</td>
<td>F (2, 86)=28.321, p=&lt;0.001</td>
<td>F (1, 87)=0.086, p=0.861</td>
<td>F (2, 86)=0.112, p=0.926</td>
</tr>
<tr>
<td>BSQ1</td>
<td>F (2, 111)=66.789, p=&lt;0.001</td>
<td>F (1, 112)=0.059, p=0.820</td>
<td>F (2, 111)=0.899, p=0.612</td>
</tr>
<tr>
<td>ACQ</td>
<td>F (2, 111)=58.273, p=&lt;0.001</td>
<td>F (1, 112)=0.019, p=0.914</td>
<td>F (2, 111)=0.578, p=0.734</td>
</tr>
<tr>
<td>MI</td>
<td>F (2, 111)=39.805, p=&lt;0.001</td>
<td>F (1, 112)=0.415, p=0.527</td>
<td>F (2, 111)=0.926, p=0.605</td>
</tr>
<tr>
<td>SCL-90 Anx</td>
<td>F (2, 111)=45.702, p=&lt;0.001</td>
<td>F (1, 112)=0.148, p=0.743</td>
<td>F (2, 111)=1.206, p=0.491</td>
</tr>
<tr>
<td>SCL-90 Pho</td>
<td>F (2, 111)=33.398, p=&lt;0.001</td>
<td>F (1, 112)=0.084, p=0.842</td>
<td>F (2, 111)=0.722, p=0.650</td>
</tr>
<tr>
<td>SCL-90 Dep</td>
<td>F (2, 111)=22.132, p=&lt;0.001</td>
<td>F (1, 112)=0.082, p=0.849</td>
<td>F (2, 111)=0.411, p=0.768</td>
</tr>
<tr>
<td>MOS-SF-20 Mh</td>
<td>F (2, 111)=31.287, p=&lt;0.001</td>
<td>F (1, 112)=0.246, p=0.646</td>
<td>F (2, 111)=0.721, p=0.633</td>
</tr>
<tr>
<td>MASTERY*</td>
<td>F (2, 86)=11.400, p=&lt;0.009</td>
<td>F (1, 87)=2.054, p=0.168</td>
<td>F (2, 86)=0.453, p=0.747</td>
</tr>
</tbody>
</table>

Note. PDSS-SR = Panic Disorder Severity Scale-Self Report; BSQ1 = Body Sensation Questionnaire; ACQ = Agoraphobic Cognitions Questionnaire, total score; MI = Mobility Inventory, total score; SCL-90 = Symptom Check-List: Anx = anxiety; Pho = phobic anxiety; Dep. = depression; MOS-SF-20 = Medical Outcomes Study Short-Form General Health Survey (SF-20): Mh = mental health.
* based on n=89 (the PDSS-SR and MASTERY were not used on the first 3 courses).
control their panic attacks themselves. In the absence of data on medication use after baseline assessment, the possible interactions of medication use with psychological treatment remain unknown.

Thirdly, the present study did not include a control group. Thus, it is not certain whether the effects found in this study were due to the preventive course.

Fourthly, the study did not account for possible differences in outcome between the 12 community mental health centres which offered the course.

Fifthly, because the intervention is multi-component, it cannot be known which of the components may have been effective.

Finally, the results may be biased if people of the intended target population who did not participate in the course or participated in the course, but not in the study, differed from those who did.

**CONCLUSIONS**

People with sub-threshold PD and mild PD may benefit from a preventive group intervention. The short version is as effective as the long version, but is likely to be associated with fewer costs and greater acceptability. Future, randomized, controlled trials using diagnostic assessments are needed to confirm the present findings.

**ACKNOWLEDGEMENTS**

The study was financially supported by the Health Insurance Company NUTS/OHRA (Amsterdam; grant # SNO-T-04-30) awarded to the third author.

We are indebted to Jessica Herzmanatus (GGNet) and Rianne van der Zanden (Trimbos Institute) for their help with the design and development of the ‘Don’t Panic’ intervention. We also thank the trainers and trainees for their valuable help in making this study possible.
REFERENCES


5. Reed V, Wittchen HU. DSM IV panic attacks and panic disorder in a community sample of adolescents and young adults: how specific are panic attacks? J Psychiatr Res. 1998;32:335-345.


**Effects and feasibility of a preventive intervention**

**DON’T PANIC**

**EFFECTIVENESS OF A PREVENTIVE INTERVENTION FOR PANIC SYMPTOMS**

**Results of a pilot study**

**Introduction**
- Panic disorder is a serious DSM-IV axis I disorder affecting 2.2% of the people in the Netherlands each year.
- Panic disorder negatively affects multiple life domains and the costs to society are high.
- It is estimated that the prevalence of people with panic symptoms is high.
- Having panic symptoms increases the risk of developing a panic disorder.
- Therefore, prevention is important.
- The course ‘Don’t Panic’ is a preventive intervention and can be used as a first step in a stepped-care model in mental health.
- A short course (8 sessions) may be equal effective as a long course (12 sessions) with the same elements.

**Intervention**
- 8 or 12 group sessions of 2 hours which contain:
  - Psycho-education
  - Changing life-style
  - Managing stress
  - Relaxation training
  - Cognitive restructuring
  - Interceptive exposure
  - ’In vivo’ exposure
  - Relapse prevention
- 6 - 10 participants per group.

**Study**
- One-group pre-post design.
- Setting: 12 community mental health centres in the Netherlands.
- Outcome measures:
  - Panic symptoms (PDSS, BSQ, SCL-90 ans)
  - Symptoms of agoraphobia (ACQ, M1, SCL-90 pho)
  - Mental health-related quality of life (MOS-SF-20 mhl)
  - Depressive symptoms (SCL-90 dep)
- Analyses: Intention to Treat.
- Measurements:
  - Before intervention (T0)
  - After intervention (T1)
  - Follow-up 6 months after intervention (T2)

**Baseline-characteristics**
- 114 participants.
- 78.1% female.
- 41.7 years of age (M).

**Results**
- The participants of the course showed a significant reduction in all the outcome measures.
- Large effect sizes on the outcome measures at T1.
- No significant differences in effect between the 8 and the 12 version.
- Effects remained in tact at follow-up.

**Main conclusions**
- Subjects with subclinical symptoms of panic disorder and mild panic disorder can benefit from this preventive intervention.
- The short version is as effective as the long version, but is likely to be associated with fewer costs.

**Effect sizes (d) outcome measures at T1**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDSS</td>
<td>1.17</td>
<td>1.35</td>
<td>0.94</td>
</tr>
<tr>
<td>BSQ</td>
<td>0.94</td>
<td>0.84</td>
<td>0.66</td>
</tr>
<tr>
<td>SCL-90 anx</td>
<td>0.67</td>
<td>0.65</td>
<td>0.50</td>
</tr>
<tr>
<td>ACQ</td>
<td>0.75</td>
<td>0.70</td>
<td>0.65</td>
</tr>
<tr>
<td>M1</td>
<td>0.70</td>
<td>0.61</td>
<td>0.55</td>
</tr>
<tr>
<td>SCL-90 pho</td>
<td>0.70</td>
<td>0.65</td>
<td>0.50</td>
</tr>
<tr>
<td>MOS-SF-20 mhl</td>
<td>0.65</td>
<td>0.60</td>
<td>0.55</td>
</tr>
<tr>
<td>SCL-90 dep</td>
<td>0.60</td>
<td>0.55</td>
<td>0.50</td>
</tr>
</tbody>
</table>

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Posterontwerp: Rolf van Dijk Vormgeving, Amstel
Chapter 3

Early intervention in panic: randomized controlled trial and cost-effectiveness analysis

Early intervention in panic: randomized controlled trial and cost-effectiveness analysis.
Trials. 2008;9(67)
ABSTRACT

Background: Panic disorder (PD) is a common, severe and persistent mental disorder, associated with a high degree of distress and occupational and social disability. A substantial proportion of the population experiences subthreshold and mild PD and is at risk of developing a chronic PD. A promising intervention, aimed at preventing panic disorder onset and reducing panic symptoms, is the ‘Don’t Panic’ course. It consists of eight sessions of two hours each. The purpose of this study is to evaluate the effectiveness of this early intervention - based on cognitive behavioural principles - on the reduction of panic disorder symptomatology. We predict that the experimental condition show superior clinical and economic outcomes relative to a waitlisted control group.

Methods/design: A pragmatic, pre-post, two-group, multi-site, randomized controlled trial of the intervention will be conducted with a naturalistic follow-up at six months in the intervention group. The participants are recruited from the general population and are randomized to the intervention or a waitlist control group. The intervention is offered by community mental health centres. Included are people over 18 years of age with subthreshold or mild panic disorder, defined as having symptoms of PD falling below the cut-off of 13 on the Panic Disorder Severity Scale-Self Report (PDSS-SR). Primary outcomes are panic disorder and panic symptoms. Secondary outcomes are symptoms of agoraphobia, anxiety, cognitive aspects of panic disorder, depressive symptoms, mastery, health-related quality of life, and cost-effectiveness. We will examine the following variables as potential mediators: cognitive aspects of panic disorder, symptoms of agoraphobia, anxiety and mastery. Potential moderating variables are: socio-demographic characteristics, panic disorder, agoraphobia, treatment credibility and mastery.

Discussion: This study was designed to evaluate the (cost) effectiveness of an early intervention based on cognitive behavioural principles. The strong external validity is one of the strengths of the study design.

Trial registration: Current Controlled Trials ISRCTN33407455.
BACKGROUND

Panic disorder (PD) affects 2% to 3% of the adult population each year\(^1\)-\(^3\), and is associated with a large burden of disease, considerable medical consumption and extensive loss of productivity\(^4\)-\(^7\). The incidence of PD is high (about 35% of all PD cases are new cases, having emerged only in the last year\(^1\)), indicating the importance of prevention and early intervention in PD.

A substantial proportion of the population suffers from subthreshold PD\(^8\)-\(^10\). Subthreshold PD can be defined as the presence of some symptoms of PD, not meeting the DSM-IV diagnostic criteria. In a study reported by Norton, Dorward and Cox\(^11\), 35.9% of the 256 presumably normal subjects reported experiencing one or more panic attacks in the past year, with 22.7% experiencing one or more panic attacks within the past three weeks. These subjects may be at risk of developing full-blown PD\(^12,13\).

PD sufferers are often not recognized as such\(^4\). Furthermore, although there are effective treatments for PD\(^14\), PD sufferers do not always receive empirically supported treatments; even if this were the case, the proportion of burden averted would still be low\(^15\). In addition, it usually takes many years before treatment is sought, and when not properly treated the prognosis is poor and the disorder may become chronic\(^16\). Prevention and early intervention in PD are therefore of great interest, and a panic prevention and early intervention program delivered to subjects with subthreshold or mild PD may decrease current panic disorder symptomatology.

Studies on prevention and early intervention in anxiety disorders indicate that prevention of anxiety disorders through cognitive-behavioural interventions can be successful\(^17\)-\(^19\). Only a few studies have been conducted in this field. Gardenswartz and Craske\(^20\) tested a prevention program for panic disorder. Participants consisted of college students who had experienced a panic attack in the last 12 months and had at least moderate anxiety sensitivity (ASI score of 16 or higher\(^21\)), but did not meet the criteria for panic disorder (CIDI)\(^22\). They were randomly assigned to either a one-day prevention workshop (\(n = 55\)) or a wait-list control (\(n = 66\)). The one-day (five-hour) workshop entailed psycho-education, breathing retraining, cognitive restructuring, interoceptive exposure and ‘in vivo’ exposure. At six-month follow-up nine participants (13.6%) from the wait-list group and only one participant (1.8%) from the workshop group had developed panic disorder, indicating a favourable treatment response.

In a study by Swinson, Soulios, Cox, and Kuch\(^23\), 33 adults with panic attacks seen in two emergency rooms were randomly assigned to groups receiving reassurance (\(n = 16\)) or exposure instruction (\(n = 17\)). Subjects who had received the exposure instruction significantly improved over the six-month follow-up period for symptoms of depression, avoidance, and panic frequency, whereas subjects receiving reassurance did not improve for any of these variables.
Despite methodological limitations, such as limited generalizability, small sample size and short follow-up periods, the results of these studies suggest that prevention of panic disorder is a promising option. The aim of this study is to examine the effectiveness of an early intervention for panic symptoms in a sample of self-referred people presenting with subthreshold or mild PD in a randomized controlled trial. We predict that the intervention will show superior effects in reducing panic disorder symptomatology, compared to a waitlisted control group. Furthermore, an economic analysis will be performed to assess the cost-effectiveness of the intervention.

**METHODS**

**Study design**
The study was designed as a pragmatic, multi-site, randomized controlled trial of the ‘Don’t Panic’ course versus a wait-list control group. Measurements were taken at baseline measurement (T0) followed by a posttest measurement after three months (T1). To monitor effect maintenance over time, the experimental group underwent a prolonged follow-up measurement nine months after baseline, i.e., six months after the end of the intervention (T2). The study was designed to mimic the Dutch health care system as naturalistically as possible in terms of patient recruitment and the manner in which intake, offering the intervention, and monitoring outcomes are conducted. This was done to enhance external validity. The randomization took place after administration of the International Neuropsychiatric Interview Plus (MINI-Plus)\(^2\), and was carried out centrally by an independent third party. A blocked randomization scheme was used, stratified by mental health centre, subthreshold PD versus mild PD, and by presence versus absence of co-occurring agoraphobia. The latter was included because it was assumed that agoraphobia may be a prognostically relevant factor for outcome in PD. This procedure ensures that participants with and without PD or agoraphobia were equally distributed across both trial arms. See Figure 1 for participants’ flow through the study. The trial protocol was approved by an independent medical ethics committee (METIGG).

**Sample size**
Power analysis indicated that 129 participants per condition are required in order to detect a difference in symptom reduction, equivalent to a standardized effect size of at least 0.35 in a two-sided test at alpha =0.05 and a power of (1-beta)=0.80.

**Study sample**
Participants were recruited from the general adult population in the Netherlands. They were eligible when over 18 years of age and presenting with subthreshold or mild panic
disorder, defined as having symptoms of PD falling below the cut-off of 13 on the Panic Disorder Severity Scale-Self Report (PDSS-SR)\textsuperscript{25,26}. Exclusion criteria were more severe PD (PDSS-SR \textgreater= 13), other current severe psychiatric symptoms or social problems, suicidal intention warranting treatment or likely to interfere with participation in the group course, and current psychological treatment for PD-related complaints. Other exclusion criteria were illness requiring immediate medical attention, and inability to function independently as well as in a group. People meeting one of the exclusion criteria were advised to seek regular treatment. If a participant used medication for anxiety or depression, it was agreed not to change the medication during the study period. Following a thorough explanation of the study procedures, written informed consent was obtained.

\textbf{Figure 1.}

Participants’ flow through the study

Recruitment
Participants were recruited from the general population through media announcements and via the internet. For screening, the standard procedures employed by the Community Mental Health Centers were used. Firstly, people who showed interest were given more information about the course and the study. They also had an initial screening interview by telephone to ascertain the presence of panic symptoms. Secondly, potential participants had an interview with an experienced psychologist from a Community Mental Health Centre. In this interview, the exclusion criteria as described above were checked. In addition, potential participants were interviewed by trained interviewers from the Trimbos Institute (Netherlands Institute of Mental Health and Addiction) using the MINI-Plus. This was done to assess the DSM-IV PD status, the presence of current co-morbid agoraphobia, and to exclude the presence of current severe major depressive disorder.

Interventions
We developed an early intervention for panic symptoms, called the ‘Don’t panic’ course. The course is based on cognitive-behavioural principles and makes use of interventions that have appeared effective in the treatment of the full-blown disorder. This intervention was developed specifically for adults. It consists of eight weekly sessions of two hours each in groups of six to 12 participants. The ‘Don’t panic’ course makes use of a course manual, to be used by the psychologist and prevention worker offering the intervention, and an accompanying workbook for the participants. The course instructors received a one-day training in offering the course and working with the course manual, to ensure integrity of the intervention delivery. Participants were taught to examine their panic attacks and the possible causes, to use techniques to influence their anxiety, and to develop skills to improve how they cope with panic attacks. The course includes (a) a psycho-educational element about the nature and physiology of anxiety and panic attacks, (b) life-style changes to improve physical condition, (c) stress management to prevent constant tension by learning effective ways to cope with stress, (d) relaxation training to reduce physiological arousal, (e) cognitive restructuring to challenge and correct dysfunctional cognitions of panic and anxiety, (f) interoceptive exposure to reduce the fear of somatic sensations, (g) ‘in vivo’ exposure to reduce agoraphobic avoidance, and (h) techniques aimed at relapse prevention. During the course the participants had to evaluate their progress. After three months following completion of the course a booster session was offered. Each session was structured to include a discussion of homework assignments, feedback, rehearsals, information about the upcoming topic and practical skills training. The intervention was extensively pilot-tested before entering the clinical trial stage. The control condition consisted of a waiting list. Waitlisted people were told that they could start the course after four months. They were not kept waiting for the extended follow-up for ethical reasons.
Instruments
The instruments used are well validated and frequently applied in international studies. Table 1 represents the measurements conducted at the different assessment times. Most of the self-report questionnaires were used for all three measurements and completed at home. The MINI-Plus was conducted by telephone at T0 and T1.

Table 1. Instruments at different assessment times

<table>
<thead>
<tr>
<th>Instrument</th>
<th>T0</th>
<th>T1 (3 months)</th>
<th>T2 (9 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDSS-SR</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>MINI-Plus</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>HADS-Anx.</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>PAI</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>BDI-II</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Mastery</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>TIC-P</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Evaluation</td>
<td></td>
<td></td>
<td>x</td>
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<td>Demographics</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>AUDIT</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>TCQ</td>
<td></td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

PDSS-SR: Panic Disorder Severity Scale-Self Report, MINI-Plus: Mini International Neuropsychiatric Interview-Plus, MI: Mobility Inventory, HADS-Anx.: Hospital Anxiety and Depression Scale, subscale Anxiety, PAI: Panic Appraisal Inventory, BDI-II: Beck Depression Inventory-second edition, EQ-5D: EuroQol Questionnaire, TIC-P: Trimbos and Institute of Medical Technology Assessment Questionnaire on Costs Associated with Psychiatric Illness, AUDIT: Alcohol Use Disorders Identification Test, TCQ: Treatment Credibility Questionnaire.

Primary outcome measures
Primary outcome measures include the severity of panic symptoms and PD diagnoses.

Severity of panic symptoms
For severity of panic symptoms the Dutch adaptation of the PDSS-SR\textsuperscript{25,32} was used. The PDSS-SR contains seven items that assess the severity of seven dimensions of panic disorder and
associated symptoms: 1) frequency of panic attacks; 2) distress during panic attacks; 3) anticipatory anxiety (worry about future panic attacks); 4) agoraphobic fear and avoidance; 5) interoceptive fear and avoidance (i.e., apprehension and avoidance of bodily sensations); 6) impairment of or interference in work functioning; and 7) impairment of or interference in social functioning. The PDSS-SR generates a total score ranging from 0 to 28, with a higher score indicating more severe panic symptoms. The questionnaire has good psychometric properties (Cronbach’s alpha=0.92; intraclass correlation coefficient=0.81)\(^3\). A cut-off score of eight may discriminate between the presence or absence of current DSM-IV panic disorder\(^25,32\) and a cut-off score of thirteen may discriminate between mild and severe panic disorder\(^26,32\).

**Diagnosis**
To assess the DSM-IV panic disorder status the Dutch version of MINI-Plus\(^24,34\) was used. The MINI-Plus is a short, structured, diagnostic interview for DSM-IV and ICD-10 psychiatric disorders, designed for use by professional interviewers. Validation of the MINI in relation to the Structured Clinical Interview for DSM-III-R Patient Version and the Composite International Diagnostic Interview showed good to very good kappa values\(^24\). To exclude serious major depressive disorder this section was supplemented with the Sheehan Disability Scale\(^35\). Subjects who reported at least two areas of role functioning with severe role impairment due to a depressive disorder were excluded from the study. The interviews were conducted by experienced interviewers who received one day’s training. The interviews were conducted by telephone, as several findings provide qualified justification for this mode of assessing psychiatric disorders\(^36,37\). The interviewers were blind with respect to the randomization status of the participants.

**Secondary outcome measures**
Secondary outcome measures include symptoms of agoraphobia, anxiety symptoms, cognitive measure for panic, depressive symptoms, perceived control, quality of life and cost-effectiveness.

**Symptoms of agoraphobia**
For symptoms of agoraphobia the Dutch adaptation of the Mobility Inventory (MI)\(^38,39\) was used. The MI assesses agoraphobic avoidance. The total score ranges from 1 to 5, with a higher score indicating more avoidance. The MI has been found to have good test-retest reliability, high internal consistencies, and reasonably concurrent validity\(^38,39\).

**Anxiety symptoms**
The subscale for anxiety of the Dutch version of the Hospital Anxiety and Depression Scale (HADS) was used to indicate the possible presence of anxiety states. The HADS was developed
as a brief self-report screening scale to detect states of depression and anxiety in the setting of a medical out-patient clinic\(^4\). A validation study of the Dutch version of the HADS by Spinhoven et al.\(^4\) confirmed the two-factor structure and showed \(\alpha\)'s ranging from 0.71 - 0.90 for the total scale and both subscales. The subscale for anxiety consists of seven items with a score range of 0-21. A high score means a higher state of anxiety.

**Cognitive measure for panic**

As a cognitive measure for panic disorder the Dutch version of the Panic Appraisal Inventory (PAI)\(^4\) was used. The PAI measures cognitive aspects of panic disorder, such as (PAI-anticipation) perceived likelihood of panic occurrence, (PAI-consequences) perceived negative consequences of panic occurrence, and (PAI-coping) perceived self-efficacy in coping with panic. Each of the three subscales of the PAI consists of 15 items; the scale score ranges from 0 to 100, and a higher score means a more negative cognitive state. The PAI has excellent psychometric properties; it has been shown to be reliable, valid and quite sensitive to change after therapy\(^4\).

**Depressive symptoms**

The Dutch version of the Beck Depression Inventory, second edition, (BDI-II)\(^4\) was used to assess depressive symptoms. The BDI-II is a 21-item self-report questionnaire for assessing the severity of depressive symptoms in the past week. The total score ranges from 0 to 63. A high score reflects a higher depression level. The BDI-II has good psychometric properties\(^4\).

**Perceived control**

The Dutch version of the Mastery-Scale\(^4\) was used to assess locus of control; a higher rating means greater internal locus of control, indicating more feelings of mastery. The total score ranges from 5 to 25. The Mastery-Scale has good psychometric properties\(^4\).

**Quality of life**

As a measure for quality of life the Dutch version of the EuroQol Questionnaire (EQ-5D)\(^4\) was used. It contains five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each of which is rated by the respondent as causing ‘no problems’, ‘some problems’, or ‘extreme problems’. The EQ-5D generates a total of 243 unique health states, each of which is associated with a utility score ranging from 0 (poor health) to 1 (perfect health). The EQ-5D is a validated instrument for measuring general health-related quality of life\(^4\).

**Cost-effectiveness**

For economic evaluation the following costs were examined, using parts of the Trimbos and Institute of Medical Technology Assessment Questionnaire on Costs Associated with
Psychiatric Illness (TIC-P)\textsuperscript{51}: costs directly related to health care, indirect health care related costs (out-of-pocket costs, costs of informal care), direct costs outside health care (monetary value of production losses caused by absence and reduced productivity).

Additional measures
To examine the feasibility and acceptability of the intervention, questionnaires were used to evaluate the course by the participants (e.g., questions to evaluate organizational aspects, coaching, content, group sessions, and workbook) at posttest. To collect demographic information pertaining to the participants, questions concerning gender, age, nationality, living situation, education and occupation were added to the self-report questionnaires. Furthermore, the AUDIT (Alcohol Use Disorders Identification Test)\textsuperscript{52} was used to assess alcohol use and the TCQ (Treatment Credibility Questionnaire)\textsuperscript{53} was used for treatment credibility. Both questionnaires have good psychometric properties\textsuperscript{54,55} and were used as possible predictor variables.

Analyses
All analyses were conducted in agreement with the intention to treat principle\textsuperscript{56}, hence all participants were analyzed in the condition to which they were randomized, and missing endpoints at follow-up were imputed using a regression model with the best available predictors of outcome and the best predictors for dropout. The first set of predictors is required to get the most precise estimates for the missing values; the latter to correct for bias that may stem from differential loss-to-follow-up associated with T0 variables\textsuperscript{57}. In all analyses on effectiveness, we controlled for the clustering of data caused by the multi-site character of the study. Clustering violates the assumption of independence of observations, and may thus affect standard errors and \( P \) values. So-called ‘robust standard errors’ and correct \( P \) values were obtained using the first-order Taylor series linearization method. All analyses were conducted with Stata 9.0\textsuperscript{58}.

For the primary outcome on PDSS-SR, a Gaussian regression model was used to test the hypothesis of superior intervention effects in the experimental arm compared to the waitlist control group. We calculated between-group effect sizes at posttest by subtracting the mean posttest score of each condition and dividing the difference by the pooled standard deviation (Cohen’s \( d \)). In the field of psychological interventions, effect sizes in the range of 0.00 to 0.32 are regarded as small, while effect sizes of 0.33 to 0.55 are moderate, and effect sizes of 0.56 to 1.2 are large\textsuperscript{59}.

As primary outcome we also compared the proportion of participants manifesting a clinically significant change on the PDSS-SR (responders) across the two groups. Clinically significant change was defined according to the criteria proposed by Jacobson and Truax\textsuperscript{60}: a change should move from a dysfunctional distribution to a functional one, and the change should be
statistically reliable in the sense that the observed change cannot be put down to measurement error in the PDSS-SR. Because we studied a population with subthreshold and mild PD, we considered scores below one standard deviation of the mean pretest score on the PDSS-SR as falling within the functional range\textsuperscript{61}. This binary outcome was then used to obtain the odds ratio (OR) using a logistic regression of the binary outcome on the intervention dummy and the numbers-to-be-treated (NNT) using Gaussian regression.

The sample can be divided in two groups: people with relatively mild manifestations of MINI-DSM-IV panic disorder and those with subthreshold manifestations not meeting the diagnostic criteria. When we focus on the latter group: people at risk of developing panic disorder, we can look at how many of these persons developed PD meeting the diagnostic criteria of the DSM-IV at T1. When we pay attention to the group with mild PD, we can see how many of these persons became PD-free at T1. For the primary outcome on the MINI-Plus we compared the proportion of success across the two groups. Success was defined as: (a) the participant had no PD at T0 and stayed PD free at T1 or (b) the participant had mild PD at T0 and no PD at T1. This yields a binary outcome where failure is coded 0, and success is coded 1. In a next step, this binary outcome was used to obtain the OR and the NNT.

The demographic and clinical characteristics of responders versus non-responders, and success versus failure, were compared using Student’s \( t \) test for independent groups or Pearson’s chi-squared tests when appropriate.

For the secondary outcomes on continuous measurement scales, a Gaussian regression model was used to test the hypothesis of superior intervention effects in the experimental arm compared to the wait-list control group. Furthermore, the between-group effect sizes (Cohen’s \( d \)) were calculated. To test the maintenance of the effects at six-month follow-up we used a paired-samples \( t \) test to analyze the difference in mean score of the self-report measures in the experimental group from T0 to T1, T0 to T2 and T1 to T2.

To provide a more comprehensive picture of the effects of the intervention, results for the outcomes will also be presented for completers only (defined as participants who attended at least six sessions).

The following variables will be examined as potential mediators: cognitive aspects of panic disorder, symptoms of agoraphobia, anxiety and mastery. Furthermore, potential moderating variables (e.g., socio-demographic characteristics, panic disorder, agoraphobia, treatment credibility and mastery) will be analyzed.

The following costs are examined for economic evaluation: costs directly related to health care, indirect health care related costs (out-of-pocket costs, costs of informal care), direct costs outside health care (monetary value of production losses caused by absence and reduced productivity), as measured with the TIC-P. The mean total costs for each of the conditions at baseline and T1 were calculated. Then the pre-post difference in costs were calculated to obtain the increase (or decrease) of costs over time in each of the conditions.

First, we observed how many participants presented with a clinically significant change on
the PDSS-SR across the two groups. The incremental cost-effectiveness ratio (ICER) was calculated as the incremental costs for a health gain of a clinically significant change over three months. Next, we observed how many people stayed PD free at T1. The ICER was calculated as the incremental costs for a health gain of a PD-free survival over three months. Furthermore, we calculated the incremental cost-utility ratio (ICUR) across the experimental and control condition. The ICUR represents the incremental costs (or savings) per QALY (Quality Adjusted Life Years, assessed with the EQ-5D) gained in the experimental condition relative to the control condition. By calculating ICUR the results can be compared to other health care interventions. In all cases, uncertainty was assessed by means of non-parametric bootstrapping (2,500 times) of the data of the individual respondents. All tests were conducted using a two-sided significance level at $\alpha < 0.05$.

**DISCUSSION**

The purpose of this study is to evaluate the effectiveness of this early intervention based on cognitive behavioural principles on the reduction of panic disorder symptomatology. Furthermore, cost-effectiveness of the intervention is evaluated. We predicted that the experimental condition would show superior effects in reducing panic symptoms, improving quality of life and will be cost-effective despite the additional costs introduced by offering the ‘Don’t Panic’ intervention in the first place. This may be regarded to be an important finding, because, to our knowledge, this is the first study that examines the effectiveness of an early intervention for self-referred adults with subthreshold or mild panic disorder, offered by community mental health centres.

**Strengths and limitations**

We changed the original protocol by including people with mild PD (PDSS < 13) and, as a consequence, not excluding participants with PD according to the MINI-Plus. People with mild PD are known to be shy in asking professional help. A low threshold intervention may appear accessible and acceptable for these people. In the Dutch mental health care system people with subthreshold or mild mental disorders are usually offered courses as a first step in a stepped-care model in mental health\textsuperscript{62-64}. To strengthen the external validity of the trial we decided to include people with mild PD. Furthermore, the results may be highly generalizable as the intervention is studied in its natural setting and the recruitment strategies of both the study and the community mental health centres that offer the course are very similar. Another strength of this trial is the use of an structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders (MINI-Plus). This makes it possible to analyze changes in PD status, and for randomization to be stratified by subthreshold PD versus mild PD, and by presence...
versus absence of co-occurring agoraphobia. The latter was done because it was assumed that agoraphobia is a prognostic relevant factor for treatment response in PD.

We recognize a number of limitations in this study. First, because of the absence of a placebo control, it is not clear whether nonspecific components of the intervention, such as social cohesion and expectation of gain contribute to the possible early intervention effect. Future research should use placebo controlled designs to overcome this problem. Secondly, the time available to study a change in PD status was only three months. For ethical reasons the control group received the intervention a few weeks after T1. For future research to study a change in PD status an extended period is advised. Thirdly, because of financial limitations we could not raise the sample size, so the change of protocol by including mild PD caused a lack of power to analyze a reduction of incidence of PD according to the MINI-Plus. Fourthly, there is no control condition at six-month follow-up after the course. Therefore, definite conclusions that the possible effects at six-month follow-up may be related to the intervention are not allowed. Finally, the extended follow-up period was only six months following the conclusion of the course, but longer follow-up periods are needed to know how long the possible effects will persist.

Notwithstanding the limitations, the development and research of an early intervention in panic disorder - a severe and persistent mental disorder, associated with a large burden of disease and extensive economic costs - is of the utmost importance.

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