Influencing panic : experimental and clinical studies into determinants of panic severity

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The research presented in this thesis was conducted at the Academic Anxiety Center Maastricht, Mondriaan, School for Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands.

For my parents
For Gabriel
For Anna–Laura and Ella-Julie

Paranimfen:
Ilse Coulier
Thea Overbeek

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Chapter One

Introduction

Daily life in a patient with Panic Disorder

Patient A., a thirty-year-old woman, was referred to the Academic Anxiety Center (AAC), a tertiary outpatient setting in Maastricht. Since several years, patient A experienced panic attacks both at home and outdoors. Palpitations, an accelerated heart rate, the feeling of choking and dizziness were the principal physical symptoms during the panic attacks. Because these symptoms could be so severe, patient A believed she was going to die during a panic attack. Gradually she started avoiding situations she perceived as dangerous since getting help, or escaping, would not be possible if she would experience a panic attack. Convinced that she had a heart disease, she frequently visited the night care, the emergency room, the cardiologist and the neurologist but each time she was told 'everything was fine' and that 'the symptoms were due to stress'. Patient A was also a weekly 'client' of the general practitioner who now referred her for a diagnostic evaluation and, if possible, treatment.

Patient A first received a thorough diagnostic evaluation. The evaluation included a history of the present illness and current symptoms, past psychiatric history, review of previous treatments, personal and social history including major life events, occupational history and a family history with specific attention for anxiety disorders. There was also regard for the developmental history and possible stressful events in the months before the onset of panic. Next to the full assessment of the features of panic disorder and agoraphobia, the presence of other mental conditions was evaluated. Before her 25th birthday, patient A had never experienced psychiatric com-plaints. Five years ago, however, she experienced her first panic attack in a shopping mall. Looking back this was a stressful time as she was just divorced and had to take care of her two little children all by herself. Nevertheless, just before the panic attack, she was relaxed and enjoining herself with her friends. Patient A was brought to the emergency room where an electrocardiogram was performed. After he physician reassured her that there was nothing serious going on, he prescribed her a benzodiazepine, Oxazepam, and advised her 'to cut down the stress'. Patient A only took one tablet of Oxazepam as she reacted with such an increased feeling of lightheadedness, it frightened her even more. The general practitioner next prescribed the antidepressant Fluoxetine, an SSRI, but after reading the insert, with the instructions for use and a description of possible side effects, she refused to take the drug. In the years that followed, she withdrew herself from social activities and former hobbies like going shopping and spending time with her friends. Although patient A was a devoted runner, she stopped doing exercise, as the acceleration of her heart rate due to the physical effort, resembled the symptoms of a panic attack. Patient A felt unfitted to accompany her children to the playground or swimming pool, which made her feel guilty. She was frequently absent at work what even-tually led to her discharge. As a single mother with no support system aside from her mother, she had already very limited financial means but they increased after she became unemployed. Patient A became more and more social isolated. Due to the combination of the panic symptoms, avoidance behavior, social isolation and financial problems, she became depressed. Patient A never received any psychological treatment. Recently her mother told her that she also has a

history of panic attacks, which were successfully treated with cognitive behavioral therapy.

Trying to find an explanation for her panic symptoms, patient A was curious about her childhood, but besides separation anxiety at young age in (kinder-garten and primary school), there was nothing striking in her development history.

The psychiatric interview included a general medical history and history of sub-stance use, a review of the patient's medications, a mental status examination. A physical examination was recently done by the general practitioner. Patient A had a negative history for medical conditions such as cardiac or respiratory pathology. She had also never taken illegal drugs. In spite of the fact that patient A declared not to take any medication, she appeared never to leave home without some 'over- the- counter' medication just in case a panic attack would occur. Patient A also always carried cookies, a bottle of water and her mobile phone and without this 'safety behavior' she would never leave her home. Before experiencing the first panic attack, patient A smoked cigarettes on a daily basis. After the first panic attack, she smoked more cigarettes in an effort to reduce the anxiety ('as self medication'), but after a panic attack occurred during smoking she quitted smoking. Patient A did not drink coffee or cola.

To support the diagnosis of panic disorder and (comorbid) depressive disorder, an evaluation through the Mini International Neuropsychiatric Interview (MINI) was administered. Psychometric evaluation at pretreatment involved the Fear Questionnaire (FQA = 25.9), the Panic and Agoraphobia Scale (PAS = 29.7) and the Montgomery-Åsberg Depression Rating Scale (MADRS = 21.3). To rule out possible general medical causes of panic symptoms like thyroid disease, a blood sample was taken. Information about former medication investigation was collected and reviewed by the psychiatrist who decided that no additional testing for medical causes of panic attacks was needed. As there was no contra- indication, a 35% CO2 challenge was administered.

Patient A was diagnosed with panic disorder with (severe) agoraphobia and a comorbid (moderate) depressive disorder. From the start, patient A made it very clear that she was not prepared to take any medication. The treatment plan consistent of psycho-education (4 group sessions) and a 1- week (5 full conse-cutive days) in vivo exposure- based behavior therapy program. During this intense week patient A devoted her days to exposure to several feared situations. At the beginning, the exposure was conducted under full coaching by an experienced behavioral therapist, but gradually the coaching was reduced and at the end she performed the assignments independently. During the following two weeks, she practiced in her home and daily environment. The psychometric evaluation two weeks after treatment showed a substantial improvement in panic symptoms, avoidance and depressive symptoms (PAS = 7.7, FQA = 8.6, MADRS = 8.1). At that time, patient A had already picked up her social activities as well as running and she was thinking about applying for a new job. After the session about relapse prevention, patient A was discharged.

How to diagnose PDA

Panic disorder (PD) is an anxiety disorder characterized by the recurrent occurrence of panic attacks and this for more than one month. Panic attacks are spells of severe fear or discomfort that have abrupt onset, 'out of the blue', without warning and for no apparent reason. Even though the duration of a panic attack is short, it usually reach a peak within 10 minutes, the symptoms cause much distress.

A panic attack is usually accompanied with a sense of imminent danger, the urge to escape and various physical or cognitive symptoms. Physical symptoms can be sweating, shaking or trembling, palpitations or accelerated heart rate, sensations of shortness of breath or smothering, feeling of choking, chest pain or discomfort, abdominal distress or nausea, lightheaded-ness or feeling faint, feeling unsteady or dizzy, depersonalization (feeling detached from oneself) or derealization (feelings of unreality), paresthesias (numbness of tingling sensations), hot flushes or chills. Cognitive symptoms can be the thought of dying, fainting, losing control or going crazy. Although PD patients share common features, there can be important individual differences in the clinical presentation. Also the frequency of panic attacks can vary widely among patients. Since panic attacks are unexpected and therefore cannot be predicted, an individual may become anxious or worried about the implications of a panic attack or concerned about when the next panic attack will occur. The persistent concern is called anticipatory anxiety and is next to the panic attacks an essential feature of panic disorder according to the DSM IV (APA, 1994).

The concern or worrying about having a new panic attack often leads to significant behavioral changes which are intended to prevent panic attacks or cope with a panic attack should one occur. Patients start avoiding situations that are perceived as dangerous or uncomfortable, often because these situations are associated with previous occurrence of panic attacks. The avoidant behavior can gradually expand to more and more situations in which having a panic attack would be embarrassing or in which escape would be difficult, such as elevators, crowded places (restaurants, shopping malls) or driving long distances). The amount of avoidance can differ substantially between individuals; from only mild levels of avoidance to extreme avoidance. Agoraphobic avoidance can lead to considerable dysfunction in several aspects of life and in severe cases even to 'homebounding' in which patients become unable to leave their ('safe') home and end up being socially isolated and often unemployed. The avoidance behavior is referred to as agoraphobia. Although agoraphobia is not a required component of panic disorder within the DSM-IV, it is very common in PD (Weissman et al., 1997).

Since panic attacks often occur in other mental and general disorders, panic disorder is only in a subset of these individuals the correct diagnosis. To make an accurate diagnosis, it is important to determine the context in which the panic attacks occur. In many psychiatric disorders (such as specific phobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder) panic attacks can be an associated feature but in contrast with PD, the panic attacks in these disorders

are triggered by a specific external stimulus, whereas in PD, the panic attacks are seen as from bodily internal origin. Caffeine (and related compounds in beverages), medications (stimulants, decongestants, agents to treat asthma, over-the-counter medications) and drugs ('intoxication with or withdrawal from') can also provoke or exacerbate symptoms of a panic attack. Therefore, only if panic attacks do not occur solely as a result of another mental disorder, general medical condition or (intoxication or withdrawal from) drugs, a concomitant diagnosis of panic disorder may be warranted.

The use of explicit diagnostic criteria and structured interviews has greatly improved diagnostic reliability of PD, basis for its syndromal validity, for the information we obtain from the PD patients about their symptoms, is subjective and entirely retrospective. To be able to study the PD symptoms better, models of panic were developed using different types of challenges to provoke panic under laboratory conditions. We call these models 'challenges' because they intentionally put the subject under strain by either manipulating of a physiological parameter or administration of a pharmacological agent. The parameter or agent that is used in order to get more insight in the underlying pathophysiology of panic disorder is believed to be directly related to the pathogenesis of panic disorder. Based on the criteria proposed by Guttmacher et al. (1983) inhalation of a vital capacity of 35% CO2 can be considered a good experimental model (Uhde and Tancer 1990 based on Guttmacher et al. 1983 and Gorman et al. 1987).

What does it mean for the individual and for society

Panic disorder is a common and often disabling mental disorder. The twelve month prevalence of PD is estimated around 1% and the lifetime prevalence rates ranges from 1,5 to 4,7 % (Mendolowiz and Stein, 2000; Norton et al., 2008; Pane – Farre et al., 2014). It is important to note that about 22,7% of people of the general population, experience a (isolated) panic attack once in their lifetime without this leading to the development of a panic disorder (Kessler et al. 2006). The gender and the age of onset of the panic disorder in-patient A, are typical in PD; the mean onset in panic disorder is 25 years and women are more at risk (about twofold) for developing PD (Kessler et al., 2006). The onset in women can range from 25 to 35 years and in men from 30 to 45 years (Wittchen and Essau, 1993,). Panic disorder has a high degree of comorbidity with other anxiety disorders like social phobia (20-75%), generalized anxiety disorder (20%), obsessive-compulsive disorder (14%) and post- traumatic stress disorder (6%) (Goisman et al., 1994; Overbeek et al., 2000; Pelissolo and Lepine, 1998). Also depression is a frequent comorbid complication of PD with lifetime comorbidity of up to 60% (Weissman et al., 1997). PD can have a great impact on several parts of daily life including social relationships, work, school, family, leisure activities and therefore cause much suffering (Katerndahl and Realini, 1997; Kessler and Frank, 1997).

Since PD is associated with multiple physical symptoms, many PD patients are convinced that they have a heart or lung disease, it is highly prevalent in primary care, occurring in 4-6% of patients. Because of the intense symptoms that

accompany panic disorder, several symptoms closely resemble a life-threatening physical illness such a myocardial infarction or acute asthma, patients visit frequently emergency rooms where they often receive extensive and extremely costly medical check-ups to rule out 'severe somatic' pathology. The fact that the treating physician has decided that these tests are necessary in combination with not receiving a conclusive explanation for their complaints, creates further anxiety and leads to 'medical shopping' and hence high health costs (Katon et al., 2002; Zaubler and Katon, 1998).

Factors that have an influence

In an effort to avoid panic attacks, to reduce the (anticipatory) anxiety and to be able 'to go out', patients with PD develop all kinds of behavior, hoping that this behavior can help them to achieve these goals. Like in the story of patient A, after experiencing an attack many PD patients start using benzodiazepines, start smoking more, start carrying medication/ bottles/ food if they have to leave their home, stop doing exercise. Smoking, however, seems to exacerbate rather than reduce panic symptoms. Comorbidity, like a concurrent depressive disorder, may also influence the severity of the panic symptoms. Next to these environmental factors, we cannot rule out the role of genetics in PD. Since the mother of patient A had panic attacks in the past, patient A has a positive familial psychiatric history, which is not uncommon in PD patients.

Common safety behaviors

Common safety behavior is behavior that provides the patient with an imme-diate feeling of safety and security, especially if the patient leaves his or her 'safe' home. This behavior includes carrying food, bottles, medication (prescribed or 'over the counter'), mobile cell phone but also 'carrying' somebody along so they never leave their home alone. Safety behavior also includes determining exit routes and checking locations of hospitals for example when they go on a holiday (Kamphuis and Telch, 1998). It is important to explore before treatment the extent of this safety behavior since it can disguise the degree of avoidance and it prevents obtaining the maximum benefit from exposure in vivo (Salkovskis et al., 1999).

Benzodiazepines

Research shows that patients with panic disorder have higher than average percentages of sedative abuse and dependence (Anthony et al., 1989; Conway et al., 2006; Kushner et al., 1990; Mirin et al., 1991; Nunes et al., 1988; Sareen et al., 2006). Although some patients experience anxiolytic effects using benzodiazepines (Bolton et al., 2006), sedatives can worsen panic symptoms since dizziness or lightheadedness, known side effects of sedatives, can resemble the symptoms accompanying a panic attack. In spite of the potential side effects of benzodiazepines, an advantage of benzodiazepines is their more rapid therapeutic response compared to antidepressants (Goddard et al., 2001; Pollack et al., 2003;

Woods et al., 1992). Their early onset of action can be useful for patients who experience very distressing symptoms and in whom a fast reductions of the panic symptoms is necessary, for instance to start CBT or in anticipation of the effect of an antidepressant. Since there is much evidence about the difficulty to diminish the dose of the benzodiazepine, the advantages and disadvantages of benzodiazepines should be carefully considered since ongoing use will lead to psychological dependence in most PD patients. There is no solid evidence in the literature to support the general idea that long-term use of benzodiazepines leads to gradually higher dosages (APA, 1990; Nagy et al., 1989; Pollack et al., 1993; Soumerai et al., 2003). However, the lack of studies following longer periods of benzodiazepine use especially in PD patients makes it difficult to draw definite conclusions about benzodiazepine tolerance. There is however no discussion in the literature about the clear risk of withdrawal symptoms and relapse into panic symptoms during the discontinuation of benzodiazepines, so caution is necessary (Ballenger et al., 1993; Pecknold and Swinson, 1986; Schweizer et al., 1990). Alprazolam (Ballenger et al., 1988; Chouinard et al., 1982; Curtis et al., 1993; Dager et al., 1992; Dunner et al., 1986; Tesar et al., 1991; Schweizer et al., 1993; Sheenan et al., 1984) and clonazepam (Moroz and Rosenbaum, 1999; Tesar et al., 1991; Valenca et al., 2003) have shown their efficacy in the treatment of PD, but diazepam and lorazepam, when given in equivalent doses, may be as effective (albeit at a cost of stronger sedative effects).

Exercise

Patient A stopped doing exercise because the acceleration of her heart rate, due to the physical exercise, resembled a panic attack. Since there are more and more data suggesting that aerobic exercise benefits patients with a depressive or anxiety disorder, exercise is also recommended in the treatment of anxiety disorders especially with a concurrent depression (Broman- Fulks et al., 2004; Stathopoulou et al., 2006;Strohle et al., 2005). Even though studies showing the positive effect of aerobic exercise on panic symptoms in PD are still scarce, the psychiatrist should nevertheless consider incorporating aerobic exercise (e.g., walking for 60 minutes or running for 20–30 minutes at least 4 days per week) in the treatment plan of PD patients since this can also be used as a form of interoceptive exposure (Esquivel et al., 2008;Stein et al., 1992).

Smoking cigarettes

Patient A already smoked cigarettes before the first panic attack, briefly smoked more cigarettes after experiencing the first panic attack in an attempt to control her anxiety and the panic attacks ('self-medication') but decided to quit smoking after experiencing a panic attack during smoking. Although all these 'steps' have been described in previous literature in an effort to elucidate the temporal pattern of the relationship between smoking and panic, the literature has given inconclusive results. There is no discussion however about the unequal proportion of PD patients that smoke cigarettes compared to patients with other anxiety disorders and to healthy people. Since the respiratory system plays a key role in maintaining the

partial pressure of carbon dioxide (pCO2), O2 and the pH within a narrow physiological range in the body, CO2 is a considered a basic factor in the control of breathing. The fact that the 35% CO2- challenge elicits the same type of panic- like symptoms with prominent respiratory symptomatology (such as breathlessness), as well in healthy subjects as in patients, suggests a link between respiration and panic attacks (Colasanti et al., 2008). This is in line with epidemiologic research that shows that the prevalence of panic disorder in COPD patients is notably increased compared to the general population (Livermore et al., 2008; Mikkelsen et al., 2004). Although the temporal pattern is still under debate, there is literature suggesting that daily smoking increases the risk for panic attacks and panic disorder. Since quitting smoking has also many benefits for the general health, smoking cessation interventions should be considered in any case if the PD patient is a smoker. Since there is evidence supporting the idea that smoking can be anxiogenic but also anxiolytic (Goodwin et al., 2005; Isensee et al., 2003), the question remains if 'smoking leads to panic' or 'panic leads to smoking'.

Genetics

Although there is growing interest in defining the genetic basis for PD, and research has led to increasing knowledge on PD and genetics, there is still not enough evidence to reach a clear conclusion about the role and extent of genetic influence in the etiology of PD. However, studies comparing the phenotype prevalence among unaffected controls' relatives with that of affected probands' relatives clearly showed that PD aggregates in some families (Goldstein et al., 1994; Goldstein et al., 1997; Horwath et al., 1995; Maier et al, 1993; Mendlewicz et al., 1993; Noyes et al., 1986). Several studies also show that healthy first- degree relatives of PD patients have an elevated CO2 reactivity that is intermediate between healthy controls without a familial PD history and PD patients, suggesting an association between genetics and CO2 hypersensitivity (Coryell, 1997; van Beek and Griez, 2000). The study of Schruers et al. (2011) suggests that the 5-HT transporter gene moderates the dose- dependent fear reaction to CO2 administration since individuals with the LL genotype showed a stronger fear reaction to CO2. The meta-analysis of Hettema et al (2001) showed an estimated heritability of 30%-40%, suggesting that the environment also contributes significantly to PD's pathogenesis. To date, the extent of the contribution of genetics versus environmental factors on PD is still not clearly defined.

Comorbidity

Research has clearly shown the large extent of comorbidity associated with panic disorder (Alonso et al., 2004; Bijl and Ravelli, 2000; Klerman et al., 1991; Sanderson and Andrews, 2002). Among PD patients, the life- time prevalence of major depression is estimated 34.7% and if agoraphobia is associated, the lifetime prevalence estimation is 38.7% (Kessler et al., 2006). It has been suggested that approximately one-third of the PD patients are depressed when they present for treatment of the panic symptoms (Lesser et al., 1989). If there is an associated depressive disorder present, the PD patient is at risk for greater impairment, more

hospitalizations, and generally more psychopathologi-cal symptoms (Bowen et al., 1994; Roy-Byrne et al., 2000). The issues concerning treatment of the PD patient with a concurrent depressive disorder, will be addressed elsewhere in this chapter.

Treating panic disorder

In the Dutch guidelines for treating panic disorder, the choice for a 'stepped care model' has been made. Patients with severe panic disorder and (severe) agoraphobia have, in addition to psychoeducation, two options; cognitive behavioral therapy (CBT) versus pharmacotherapy. In case of an associated depressive disorder, adding an antidepressant from the start of treatment is advised. Patient A however refused to take medication. To avoid problems in the therapeutic alliance and taken into account that she wasn't severely depressed, we respected her decision but we came to the agreement to assess the depressive symptoms at regular intervals, as becoming more depressed could interfere with the psychological therapy focusing on PD. If patient A had chosen to take medication instead of CBT, an SSRI (selective serotonin reuptake inhibitor) would have been prescribed. According to the guidelines the pharmacological steps in treating PD are (first) SSRIs, (second) TCAs (tricyclic antidepressant), (third) benzodiazepines and (fourth) a MAO (monoamine oxidase) inhibitor. Since PD patients easily mis-interpret physical sensations, they can be sensitive to side effects and therefore it is recommended to start with a low dose. The extent of avoidance seems to be a stronger predictor of functional impairment and quality of life than the frequency of panic attacks (Telch et al., 1995). Therefore, the aim of the treatment of PD is not only to decrease the frequency and intensity of panic attacks but also to reduce the anticipatory anxiety and the agoraphobic avoidance. Before treatment, it is crucial to establish the extent of the avoidance since the treatment is intended to minimize impairment in daily life and so to improve the quality of life. At the same time, there should be regard for the presence of 'safety- behavior' since it often masks the extent of the avoidance behavior.

An extensive body of evidence has documented the efficacy of CBT for the treatment of panic disorder (Barlow et al., 1989; Beck et al., 1992; Black et al., 1993; Clark et al., 1994; Craske et al., 1991; Craske et al., 1997; Craske et al., 2003; Kenardy et al., 2003; Klosko et al., 1990; Ost et al., 1995; Ost et al., 2004; Telch et al., 1993) and the effects are robust and durable (Butler et al., 2006; Clum et al., 1993; Gould et al., 1995, Mitte 2005; Westen and Morrison, 2001). Exposure in vivo is an essentail component of CBT. Several studies have examined the use of exposure in vivo, also called situational exposure, specifically for patients with panic disorder who also have a significant form of agoraphobia (van den Hout et al., 1994; Ito et al., 2001; Marks et al., 1993; Ost et al., 1993; Shear et al., 1994). Based on the current literature, CBT is the first choice in the treatment for panic disorder and exposure in vivo is indicated if agoraphobia is present. Exposure in vivo involves encouraging and confronting patients to expose themselves to a wide range of situations that normally provoke fear. Although there is evidence for a small advantage for the combination treatment (pharmacotherapy and CBT) versus CBT alone in the acute phase of the treat-ment, combined therapy seems not to have beneficial effect in the long run (but there is evidence that combination therapy is superior to

pharmacotherapy alone) (Furukawa et al., 2006). In practice, combination therapy is often used to assist in the resolution of severe panic symptoms at the beginning of the treatment.

If there is a co-occuring depressive disorder present, treating the depressive disorder should be an additional goal since the depression may affect the treatment and prognosis of panic disorder (Bowen et al., 1994; Roy- Byrne et al., 2000). If depressive symptoms are so severe that they interfere with the treatment for panic disorder, for example if the depressed patient has no energy to perform the exposure assignments, the depression becomes the primary focus of treatment. With regard to CBT, some evidence suggests that CBT focusing on the panic disorder, may also improve the depressive symptoms (Brown et al.,1995; Tsao et al., 1995; Tsao et al. 2005) but in these studies severe depressed patients were always excluded.

Many studies show that 12 weekly sessions of CBT, called short-term CBT, are effective in treating PD (Barlow et al., 2000; Brown and Barlow, 1995; Craske et al., 1991; Fava et al., 1995; Fava et al.; 2001). In an effort to make CBT available to more patients, and the urge to think about cost-effectiveness of treatments, there have been attempts to give CBT in a more high-density format. Results from these studies suggest that this format can be effective (Deacon and Abramowitz, 2006; Hahlweg et al., 2001).

Although a full remission of symptoms and return to a premorbid level of functioning should be the ultimate goal at the start of the treatment, some patients continue to have limited panic attacks or recurrent episodes of panic symptoms even if the treatment was perceived as successful (Bruce et al., 2005; Katschnig et al., 1996; Roy- Byrne and Cowley, 1995). Studies show that at 4–6 years post-treatment, about 30% of patients treated in a tertiary-care setting are well. Of the remaining 70 %, 40%–50% are improved but symptomatic and 20%–30% have symptoms that are the same or slightly worse (Katschnig et al., 1996; Roy- Byrne and Cowley, 1995). Before discharge, a personalized relapse prevention plan should be developed so the patient knows how to act if panic symptoms should recur.

In line with the guidelines patient A had psycho-education, CBT and a session of relapse prevention. In contrast with the guidelines, she didn't receive at least 12 weeks of CBT and she didn't take an antidepressant to treat her depression. However, according to both the post- treatment assessment and our clinical observations, panic and depressive symptoms were diminished to such an extent that patient A didn't fit the criteria of panic disorder or depressive disorder anymore.

Two questions remain, however; is a 12-week CBT program necessary to treat PD successfully or can this be intensified? In case of a comorbid depression, is adding and antidepressant necessary to treat the depression?

What do we need to improve the life of the PD patient?

Although relapse after remission is more frequent than maintained remission and improvement with lingering symptoms is more the rule than remission, treatment of PD can be effective and can improve quality of life of the individual substantially. Untreated PD can become a chronic and severe invalidating anxiety disorder with high economic costs for society. To date, the exact underlying pathophysiology of panic remains largely unknown, yet is clear that the development of the clinical presentation of PD depends on an interaction between genetic and environmental factors. More insight in the genetic determinants of susceptibility of panic, together with more knowledge on, and the identification of, the environmental factors of PD, can pave the way for new therapeutic approaches.

References

Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, de Girolamo G, Graaf R, Demyttenaere K, Gasquet I, Haro JM, Katz SJ, Kessler RC, Kovess V, Lepine JP, Ormel J, Polidori G, Russo LJ, Vilagut G, Almansa J, Arbabzadeh- Bouchez S, Autonell J, Bernal M, Buist-Bouwman MA, Codony M, Domingo-Salvany A, Ferrer M, Joo SS, Martinez-Alonso M, Matschinger H, Mazzi F, Morgan Z, Morosini P, Palacin C, Romera B, Taub N, Vollebergh WA: Disability and quality of life impact of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl 2004; 420:38– 46

American Psychiatric Association (APA), 1994. Diagnostic and Statistical Manual of Mental Disorders. Washington DC.

American Psychiatric Association: Benzodiazepine Dependence, Toxicity, and Abuse: A Task Force Report of the American Psychiatric Association. Washington, DC, American Psychiatric Association, 1990

Anthony JC, Tien AY, Petronis KR: Epidemiologic evidence on cocaine use and panic attacks. Am J Epidemiol 1989; 129:543–549

Ballenger JC, Burrows GD, DuPont RL Jr, Lesser IM, Noyes R Jr, Pecknold JC, Rifkin A, Swinson RP: Alprazolam in panic disorder and agoraphobia: results from a multicenter trial: I. efficacy in short-term treatment. Arch Gen Psychiatry 1988; 45:413–422

Ballenger JC, Pecknold J, Rickels K, Sellers EM: Medication discontinuation in panic disorder. J Clin Psychiatry 1993; 54(suppl);15–21; discussion 54(suppl):22–24

Barlow DH, Craske MG, Cerney JA, Klosko JS: Behavioral treatment of panic disorder. Behav Ther 1989; 20:261–282

Barlow DH, Gorman JM, Shear MK, Woods SW: Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. JAMA 2000; 283:2529–2536

Beck AT, Sokol L, Clark DA, Berchick R, Wright F: A crossover study of focused cognitive therapy for panic disorder. Am J Psychiatry 1992; 149:778– 783

Black DW, Wesner R, Bowers W, Gabel J: A comparison of fluvoxamine, cognitive therapy, and placebo in the treatment of panic disorder. Arch Gen Psychiatry 1993; 50:44–50

Bijl RV, Ravelli A: Current and residual functional disability associated with psychopathology: find- ings from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Psychol Med 2000; 30:657–668

Bolton J, Cox B, Clara I, Sareen J: Use of alcohol and drugs to self-medicate anxiety disorders in a nationally representative sample. J Nerv Ment Dis 2006; 194:818–825

Bowen R, South M, Hawkes J: Mood swings in patients with panic disorder. Can J Psychiatry 1994; 39:91–94

Broman-Fulks JJ, Berman ME, Rabian BA, Webster MJ: Effects of aerobic exercise on anxiety sensitivity. Behav Res Ther 2004; 42:125–136

Brown TA, Antony MM, Barlow DH: Diagnostic comorbidity in panic disorder: effect on treatment outcome and course of comorbid diagnoses following treatment. J Consult Clin Psychol 1995; 63:408–418

Brown TA, Barlow DH: Long-term outcome in cognitive-behavioral treatment of panic disorder: clinical predictors and alternative strategies for assessment. J Consult Clin Psychol 1995; 63:754– 765

Bruce SE, Yonkers KA, Otto MW, Eisen JL, Weisberg RB, Pagano M, Shea MT, Keller MB: Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. Am J Psychiatry 2005; 162:1179– 1187

Butler AC, Chapman JE, Forman EM, Beck AT: The empirical status of cognitive-behavioral ther- apy: a review of meta-analyses. Clin Psychol Rev 2006; 26:17–31

Chouinard G, Annable L, Fontaine R, Solyom L: Alprazolam in the treatment of generalized anxiety and panic disorders: a double-blind placebo-controlled study. Psychopharmacology (Berl) 1982; 77:229–233

Clark DM, Salkovskis PM, Hackmann A, Middleton H, Anastasiades P, Gelder M: A comparison of cognitive therapy, applied relaxation and imipramine in the treatment of panic disorder. Br J Psychiatry 1994; 164:759–769

Clum GA, Clum GA, Surls R: A meta-analysis of treatments for panic disorder. J Consult Clin Psychol 1993; 61:317–326

Colasanti A, Salamon E, Schruers K, van Diest R,van Duinen M, Griez EJ (2008). Carbon dioxide induced emotion and respiratory symptoms in healthy volunteers. Neuropsychopharmacology; 33(13): 3103-3110.

Conway KP, Compton W, Stinson FS, Grant BF: Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 2006; 67:247–257

Coryell, W., 1997. Hypersensitivity to carbon dioxide as a disease-specific trait marker. Biol Psychiatry 41, 259-263.

Craske MG, Brown TA, Barlow DH: Behavioral treatment of panic disorder: a two-year follow-up. Behav Ther 1991; 22:289–304

Craske MG, DeCola JP, Sachs AD, Pontillo DC: Panic control treatment for agoraphobia. J Anxiety Disord 2003; 17:321–333

Craske MG, Rowe M, Lewin M, Noriega-Dimitri R: Interoceptive exposure versus breathing retraining within cognitive-behavioural therapy for panic disorder with agoraphobia. Br J Clin Psychol 1997; 36(part 1):85–99

Curtis GC, Massana J, Udina C, Ayuso JL, Cassano GB, Perugi G: Maintenance drug therapy of panic disorder. J Psychiatr Res 1993; 27(suppl 1):127–142

Dager SR, Roy-Byrne P, Hendrickson H, Cowley DS, Avery DH, Hall KC, Dunner DL: Long-term outcome of panic states during double-blind treatment and after withdrawal of alprazolam and placebo. Ann Clin Psychiatry 1992; 4:251–258

Deacon B, Abramowitz J: A pilot study of two-day cognitive-behavioral therapy for panic disorder. Behav Res Ther 2006; 44:807–817

Dunner DL, Ishiki D, Avery DH, Wilson LG, Hyde TS: Effect of alprazolam and diazepam on anxiety and panic attacks in panic disorder: a controlled study. J Clin Psychiatry 1986; 47:458–460

Esquivel G, Díaz-Galvis J, Schruers K, Berlanga C, Lara-Muñoz C, Griez E. Acute exercise reduces the effects of a 35% CO2 challenge in patients with panic disorder. J Affect Disord. 2008 Apr;107(1-3):217-20.

Fava GA, Rafanelli C, Grandi S, Conti S, Ruini C, Mangelli L, Belluardo P: Long-term outcome of panic disorder with agoraphobia treated by exposure. Psychol Med 2001; 31:891–898

Fava GA, Zielezny M, Savron G, Grandi S: Long- term effects of behavioural treatment for panic disorder with agoraphobia. Br J Psychiatry 1995; 166:87–92

Furukawa TA, Watanabe N, Churchill R: Psycho- therapy plus antidepressant for panic disorder with or without agoraphobia: systematic review. Br J Psychiatry 2006; 188:305–312

Goddard AW, Brouette T, Almai A, Jetty P, Woods SW, Charney D: Early coadministration of clonazepam with sertraline for panic disorder. Arch Gen Psychiatry 2001; 58:681–686

Goisman RM, Warshaw MG, Peterson LG, et al (1994): Panic, agoraphobia, and panic disorder with agoraphobia. Data from a multicenter anxiety disorders study. The Journal of nervous and mental disease 182:72-9

Goldstein RB, Weissman MM, Adams PB, Horwath E, Lish JD, Charney D, Woods SW, Sobin C, Wickramaratne PJ. Psychiatric disorders in relatives of probands with panic disorder and/or major depression. Arch Gen Psychiatry. 1994;51:383–394.

Goldstein RB, Wickramaratne PJ, Horwath E, Weissman MM. Familial aggregation and phenomenology of 'early'-onset (at or before age 20 years) panic disorder. Arch Gen Psychiatry. 1997;54:271–278.

Goodwin RD, Lewinsohn PM, Seeley JR: Cigarette smoking and panic attacks among young adults in the community: the role of parental smoking and anxiety disorders. Biol Psychiatry 2005; 58:686–693

Gorman JM, Fyer MR, Liebowitz MR, Klein DF (1987): Pharmacologic provocation of panic attacks. In Meltzer HY (ed), Psychopharmacology: the thirth generation of progress. New York: Raven Press, pp 985-993.

Gould RA, Otto MW, Pollack MH: A meta-analysis of treatment outcome for panic disorder. Clin Psychol Rev 1995; 15:819–844

Guttmacher, L.B., Murphy, D.L., Insel, T.R., 1983. Pharmacologic models off anxiety. Compr Psychiatry 24, 312-326.

Hettema JM, Neale MC, Kendler KS. A review and meta-analysis of the genetic epidemiology of anxiety disorders. Am J Psychiatry. 2001;158:1568–1578.

Hahlweg K, Fiegenbaum W, Frank M, Schroeder B, von W, I: Short- and long-term effectiveness of an empirically supported treatment for agoraphobia. J Consult Clin Psychol 2001; 69:375–382

Horwath E, Wolk SI, Goldstein RB, Wickramaratne P, Sobin C, Adams P, Lish JD, Weissman MM. Is the comorbidity between social phobia and panic disorder due to familial cotransmission or other factors? Arch Gen Psychiatry. 1995;52:574–582.

Isensee B, Wittchen HU, Stein MB, Hofler M, Lieb R: Smoking increases the risk of panic: find- ings from a prospective community study. Arch Gen Psychiatry 2003; 60:692–700

Ito LM, de Araujo LA, Tess VL, Barros-Neto TP, Asbahr FR, Marks I: Self-exposure therapy for panic disorder with agoraphobia: randomised controlled study of external v interoceptive self-exposure. Br J Psychiatry 2001; 178:331–336

Kamphuis JH, Telch MJ: Assessment of strategies to manage or avoid perceived threats among panic disorder patients: the Texas Safety Maneuver Scale (TSMS). Clinical Psychology and Psychotherapy 1998; 5:177–186

Katerndahl DA, Realini JP: Quality of life and panic-related work disability in subjects with infrequent panic and panic disorder. J Clin Psychiatry 1997; 58:153–158

Katon WJ, Roy-Byrne P, Russo J, Cowley D: Cost- effectiveness and cost offset of a collaborative care intervention for primary care patients with panic disorder. Arch Gen Psychiatry 2002; 59:1098– 1104

Katschnig H, Amering M, Stolk JM, Ballenger JC: Predictors of quality of life in a long-term follow-up study in panic disorder patients after a clinical drug trial. Psychopharmacol Bull 1996;32:149-155

Kenardy JA, Dow MG, Johnston DW, Newman MG, Thomson A, Taylor CB: A comparison of delivery methods of cognitive-behavioral therapy for panic disorder: an international multicenter trial. J Consult Clin Psychol 2003; 71:1068–1075

Kessler RC, Chiu WT, Jin R, Ruscio AM, Shear K, Walters EE. The epidemiology of panic attacks, panic disorder and agoraphobia in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2006 Apr;63(4):415-24.

Kessler RC, Frank RG: The impact of psychiatric disorders on work loss days. Psychol Med 1997;27:861–873

Klerman GL, Weissman MM, Ouellette R, Johnson J, Greenwald S: Panic attacks in the community: social morbidity and health care utilization. JAMA 1991; 265:742–746

Klosko JS, Barlow DH, Tassinari R, Cerny JA: A comparison of alprazolam and behavior therapy in treatment of panic disorder. J Consult Clin Psychol 1990; 58:77–84

Kushner MG, Sher KJ, Beitman BD: The relation between alcohol problems and the anxiety disorders. Am J Psychiatry 1990; 147:685–695

Lesser IM, Rubin RT, Rifkin A, Swinson RP, Ballenger JC, Burrows GD, Dupont RL, Noyes R, Pecknold JC: Secondary depression in panic disorder and agoraphobia: II. dimensions of depressive symptomatology and their response to treatment. J Affect Disord 1989; 16:49–58

Livermore N, Butler JE, Sharpe L, McBain RA, Gandevia SC, McKenzie DK. Panic attacks and perception of inspiratory resistive loads in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008 Jul 1;178(1):7-12.

Maier W, Lichtermann D, Minges J, Oehrlein A, Franke P. A controlled family study in panic disorder. J Psychiatr Res. 1993;27(Suppl 1):79–87.

Marks IM, Swinson RP, Basoglu M, Kuch K, Noshirvani H, O'Sullivan G, Lelliott PT, Kirby M, McNamee G, Sengun S, Wickwire K: Alprazolam and exposure alone and combined in panic disorder with agoraphobia: a controlled study in London and Toronto. Br J Psychiatry 1993; 162:776–787

Mendlewicz J, Sevy S, Mendelbaum K. Minireview: Molecular genetics in affective illness. Life Sci. 1993;52:231–242.

Mendlowicz, M.D. and Murray B.Stein, M.D. Quality of life in Individuals With Anxiety Disorders. Am J Psychiatry 2000; 157:669-682.

Mikkelsen RL, Middelboe T, Pisinger C, Stage KB. Anxiety and depression in patients with chronic obstructive pulmonary disease (COPD). A review. Nord J Psychiatry. 2004;58(1):65-70.

Mitte K: A meta-analysis of the efficacy of psycho- and pharmacotherapy in panic disorder with and without agoraphobia. J Affect Disord 2005; 88:27– 45

Mirin SM, Weiss RD, Griffin ML, Michael JL: Psychopathology in drug abusers and their families. Compr Psychiatry 1991; 32:36–51

Moroz G, Rosenbaum JF: Efficacy, safety, and gradual discontinuation of clonazepam in panic disorder: a placebo-controlled, multicenter study using optimized dosages. J Clin Psychiatry 1999; 60:604–612

Nagy LM, Krystal JH, Woods SW, Charney DS: Clinical and medication outcome after short- term alprazolam and behavioral group treatment in panic disorder: 2.5 year naturalistic follow-up study. Arch Gen Psychiatry 1989; 46:993–999

Norton, P.J., Zvolensky, M.J., Bonn-Miller, M.O., Cox, B.J., Norton, G.R., 2008. Use of the Panic Attack Questionnaire-IV to assess non-clinical panic attacks and limited symptom panic attacks in student and community samples. J Anxiety Disord 22, 1159-1171.

Noyes R, Jr, Crowe RR, Harris EL, Hamra BJ, McChesney CM, Chaudhry DR. Relationship between panic disorder and agoraphobia. A family study. Arch Gen Psychiatry. 1986;43:227–232.

Nunes E, Quitkin F, Berman C: Panic disorder and depression in female alcoholics. J Clin Psychiatry 1988; 49:441–443

Ost LG, Westling BE: Applied relaxation vs cognitive behavior therapy in the treatment of panic disorder. Behav Res Ther 1995; 33:145–158

Ost LG, Thulin U, Ramnero J: Cognitive behavior therapy vs exposure in vivo in the treatment of panic disorder with agoraphobia (corrected from agoraphobia). Behav Res Ther 2004; 42:1105– 1127

Ost LG, Westling BE, Hellstrom K: Applied relaxation, exposure in vivo and cognitive methods in the treatment of panic disorder with agoraphobia. Behav Res Ther 1993; 31:383–394

Overbeek T, Vermetten E, Griez E (2000): Epidemiology of anxiety disorders. In Griez E, Faravelli C, Nutt D, Zohar J (eds), The European Certificate Textbook of Anxiety Disorder: In press, John Wiley & Sons.

Pane-Farre, C.A., Stender, J.P., Fenske, K., Deckert, J., Reif, A., John, U., Schmidt, C.O., Schulz, A., Lang, T., Alpers, G.W., Kircher, T., Vossbeck-Elsebusch, A.N., Grabe, H.J., Hamm, A.O., 2014. The phenomenology of the first panic attack in clinical and community-based samples. J Anxiety Disord 28, 522-529.

Pecknold JC, Swinson RP: Taper withdrawal studies with alprazolam in patients with panic disorder and agoraphobia. Psychopharmacol Bull 1986; 22:173–176

Pelissolo A, Lepine JP (1998);: Epidemiology of depression and anxiety disorders. In Montgomery SA, den Boer JA (eds), SSRI's in depression and anxiety:John Wiley and Sons Ltd, pp 1-21

Pollack MH, Simon NM, Worthington JJ, Doyle AL, Peters P, Toshkov F, Otto MW: Combined paroxetine and clonazepam treatment strategies compared to paroxetine monotherapy for panic disorder. J Psychopharmacol 2003; 17:276–282

Pollack MH, Otto MW, Tesar GE, Cohen LS, Meltzer-Brody S, Rosenbaum JF: Long-term out- come after acute treatment with alprazolam or clonazepam for panic disorder. J Clin Psychopharmacol 1993; 13:257–263

Roy-Byrne PP, Cowley DS: Course and outcome in panic disorder: a review of recent follow-up studies. Anxiety 1995; 1:150–160

Roy-Byrne PP, Stang P, Wittchen HU, Ustun B, Walters EE, Kessler RC: Lifetime panic-depression comorbidity in the National Comorbidity Survey: association with symptoms, impairment, course and help-seeking. Br J Psychiatry 2000; 176:229–235

Salkovskis PM, Clark DM, Hackmann A, Wells A, Gelder MG: An experimental investigation of the role of safety-seeking behaviours in the maintenance of panic disorder with agoraphobia. Behav Res Ther 1999; 37:559–574

Sanderson K, Andrews G: Prevalence and severity of mental health-related disability and relationship to diagnosis. Psychiatr Serv 2002; 53:80–86

Sareen J, Chartier M, Paulus MP, Stein MB: Illicit drug use and anxiety disorders: findings from two community surveys. Psychiatry Res 2006; 142:11– 17

Schruers K, Esquivel G, van Duinen M, Wichers M, Kenis G, Colasanti A, Knuts I, Goossens L, Jacobs N, van Rozendaal J, Smeets H, van Os J, Griez E., 2011. Genetic moderation of CO2-induced fear by 5-HTTLPR genotype. J Psychopharmacol 25, 37-42.

Schweizer E, Rickels K, Case WG, Greenblatt DJ: Long-term therapeutic use of benzodiazepines: II. effects of gradual taper. Arch Gen Psychiatry 1990; 47:908–915

Schweizer E, Rickels K, Weiss S, Zavodnick S: Maintenance drug treatment of panic disorder: I. results of a prospective, placebo-controlled comparison of alprazolam and imipramine. Arch Gen Psychiatry 1993; 50:51–60

Shear MK, Pilkonis PA, Cloitre M, Leon AC: Cognitive behavioral treatment compared with nonprescriptive treatment of panic disorder. Arch Gen Psychiatry 1994; 51:395–401

Sheehan DV, Coleman JH, Greenblatt DJ, Jones KJ, Levine PH, Orsulak PJ, Peterson M, Schildkraut JJ, Uzogara E, Watkins D: Some biochemical correlates of panic attacks with agoraphobia and their response to a new treatment. J Clin Psychopharmacol 1984; 4:66–75

Soumerai SB, Simoni-Wastila L, Singer C, Mah C, Gao X, Salzman C, Ross- Degnan D: Lack of relationship between long-term use of benzodiazepines and escalation to high dosages. Psychiatr Serv 2003; 54:1006–1011

Stathopoulou G, Powers MB, Berry AC, Smits JAJ, Otto MW: Exercise interventions for mental health: a quantitative and qualitative review. Clinical Psychology: Science and Practice 2006; 13:179–193

Stein JM, Papp LA, Klein DF, Cohen S, Simon J, Ross D, Martinez J, Gorman JM: Exercise toler- ance in panic disorder patients. Biol Psychiatry 1992; 32:281–287

Strohle A, Feller C, Onken M, Godemann F, Heinz A, Dimeo F: The acute antipanic activity of aerobic exercise. Am J Psychiatry 2005; 162:2376– 2378

Telch MJ, Lucas JA, Schmidt NB, Hanna HH, LaNae JT, Lucas RA: Group cognitive-behavioral treatment of panic disorder. Behav Res Ther 1993; 31:279–287

Telch MJ, Schmidt NB, Jaimez TL, Jacquin KM, Harrington PJ: Impact of cognitive-behavioral treatment on quality of life in panic disorder patients. J Consult Clin Psychol 1995; 63:823–830

Tesar GE, Rosenbaum JF, Pollack MH, Otto MW, Sachs GS, Herman JB, Cohen LS, Spier SA: Double-blind, placebo-controlled comparison of clonazepam and alprazolam for panic disorder. J Clin Psychiatry 1991; 52:69–76

Tsao JCI, Mystkowski J, Zucker B, Craske MG: Effects of cognitive behavioral therapy for panic disorder on comorbid conditions: replication and extension. Behav Ther 2002; 33: 493–509

Tsao JC, Mystkowski JL, Zucker BG, Craske MG: Impact of cognitive-behavioral therapy for panic disorder on comorbidity: a controlled investiga- tion. Behav Res Ther 2005; 43: 959–970

Udhe TW, Tancer ME (1990): Chemical models of panic: a review and critique. In Tyrer P (ed), Psychopharmacology of anxiety. London, Oxford: oxford University Press.

Valenca AM, Nardi AE, Mezzasalma MA, Nascimento I, Zin WA, Lopes FL, Versiani M: Therapeutic response to benzodiazepine in panic disorder subtypes. Sao Paulo Med J 2003; 121:77– 80

Van Beek, N., Griez, E., 2000. Reactivity to a 35% CO2 challenge in healthy first-degree relatives of patients with panic disorder. Biol Psychiatry 47, 830-835.

van den Hout M, Arntz A, Hoekstra R: Exposure re- duced agoraphobia but not panic, and cognitive therapy reduced panic but not agoraphobia. Behav Res Ther 1994; 32:447–451

Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG, Joyce PR, Karam EG, Lee CK, Lellouch J, Lépine JP, Newman SC, Oakley-Browne MA, Rubio-Stipec M, Wells JE, Wickramaratne PJ, Wittchen HU, Yeh EK.The cross-national epidemiology of panic disorder. Arch Gen Psychiatry. 1997 Apr; 54(4): 305-9

Westen D, Morrison K: A multidimensional meta- analysis of treatments for depression, panic, and generalized anxiety disorder: an empirical examination of the status of empirically supported therapies. J Consult Clin Psychol 2001; 69:875–899

Wittchen, H.U., Essau, C.A., 1993. Epidemiology of panic disorder: progress and unresolved issues. J Psychiatr Res 27 Suppl 1, 47-68.

Woods SW, Nagy LM, Koleszar AS, Krystal JH, Heninger GR, Charney DS: Controlled trial of alprazolam supplementation during imipramine treatment of panic disorder. J Clin Psychopharma- col 1992; 12:32–38

Zaubler, T.S., Katon, W., 1998. Panic disorder in the general medical setting. Journal of Psychosomatic Research 44:25-42

Chapter two

General overview

This thesis regards environmental and genetic factors in panic disorder (PD). Consecutively, we have studied the impact of environmental factors such as smoking and cognitive behavioral therapy (CBT) on panic disorder. Finally, we studied the influence of the 5-HTTLPR genotype on CBT focusing on avoidance behavior in panic disorder. With CO2 inhalations as a model to provoke panic and smoking as a technique to enhance this panic provocation, our first aim was to establish and explain the panic effects of smoking. Since the cause and temporal pattern of this comor-bidity remains controversial, we then reviewed previous literature on this topic. Next, we investigated the effect of cognitive behavioral therapy (CBT), with exposure in-vivo as the main technique, focusing on avoidance/agoraphobia in panic disorder patients. First we investigated the effect of intensified 'one week' CBT versus classical 'two-weekly' sessions. Next, we studied the effect of comorbid depression on therapy focusing on PD in depressed versus non-depressed PD patients. In these studies CBT is considered the environmental factor since we modulated the environment what lead to changes in the symptomatology of panic disorder. Finally, we examined the effect of the 5-HTTLPR genotype on CBT focusing on agoraphobia in PD patients with severe agoraphobia.

A disproportionately large number of persons with panic disorder smoke cigarettes compared to people in the general population and individuals with other anxiety disorders. Since clinical and epidemiological data suggest that cigarette smoking increases the risk for the development and maintenance of PD, it was hypothesized in **chapter 1** that cigarette smoking facilitates the emergence of CO2-induced panic ('from smoking to panic'). To test this hypothesis the 35% carbon dioxide (CO2) challenge was used to experimentally induce symptoms compatible with a panic attack. It was expected that smokers would respond stronger to the 35% CO2 challenge when compared to non-smokers. Ninety-two subjects (46 smokers and 46 non-smokers) with PD participated in the study. Several explanations for the link between smoking and panic disorder were also discussed.

Given that the link between smoking and panic disorder remains controversial and that the temporal pattern of this relationship is still a matter of debate in epidemiological studies, in **chapter 2** the literature was searched in order to determine the validity of the proposed explanatory models. The aim of the study, 24 studies were reviewed, was also to achieve a broader perspective on the link between panic and cigarette smoking and to identify the possible underlying etiologic mechanisms.

In **chapter 3** the efficacy of a brief, intensive, clinician-guided exposure program for panic disorder patients with severe agoraphobia was described and compared to a more classical form of behavioral therapy involving twice-weekly contacts with a therapist. The main outcome parameter was the agoraphobia score of the Fear Questionnaire (FQ-AGO). The outcomes of 96 patients after a 1-week intensive therapy and 98 patients after a twice-weekly therapy were compared.

The fact that cognitive behavioral therapy (CBT) is a highly effective form of treatment for panic disorder with agoraphobia (PDA) is well established. Panic disorder and depression are highly comorbid, however, and studies examining

treatment outcome for panic disorder with comorbid depression have produced mixed results. In **chapter 4**, the following hypotheses were tested; (1) a comorbid depressive disorder in PD patients results in is more severe PDA symptoms at baseline; (2) patients with and without comorbid depression improve to a comparable degree; (3) behavioral therapy for PDA result also in a clinically relevant reduction in depressive symptomatology as measured with the MADRS. Six-hundred-and-eighty-nine patients were included in the study. Out of 421 patients who entered manualized behavioral therapy, 288 completed the post-treatment assessment. One third of these 288 patients were depressed (N = 87). Those who completed the post-treatment assessment were analyzed categorically as well as dimensionally regarding the influence of depression by dividing into 2 groups (comorbid depressive disorder or not) and 3 groups (according to their MADRS-score) respectively. These groups were then compared regarding their PDA and depression outcomes at baseline and post-treatment.

The serotonin transporter length polymorphism (5 HTTLPR) is one of the most widely researched genotypes in affective neurosciences and has received much attention over the last years in the study of gene-environment (GxE) interactions. Important efforts are invested in elucidating the genetic factors that can predict the effects of pharmacological therapy for psychiatric disorders. Also relevant but much less researched is the influence of genotype on the efficacy of psychological therapy. To identify biological markers for individualization of cognitive behavior therapy is of both of theoretical and clinical interest. To date, there are very few studies investigating the role of genetic variants in the efficacy of CBT in panic disorder and agoraphobia. **Chapter 5** reports on the findings of the study that was intended to assess the extent to which the low-expression allele of the serotonin transporter gene promoter predicts a better response to exposure-based behavior therapy in patients with PDA. Ninety-nine patients with PDA underwent a 1-week in-vivo exposure-based behavior therapy program and were classified according to four allelic forms (SA, SG, LA, LG) of the 5-HTT-linked polymorphic region (5-HTTLPR) genotype. Whether the 5-HTTLPR genotype predicted change in avoidance behavior in PDA following treatment was determined, using the Fear Questionnaire as main outcome measure. It was hypothesized that the S-allele would be associated with enhanced response to therapy.

Chapter three

Cigarette smoking and 35% CO2 induced panic in panic disorder

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Abstract

Background

A disproportionately large number of persons with panic disorder (PD) smoke cigarettes compared to people in the general popula-tion and individuals with other anxiety disorders. Clinical and epidemiological data suggest that cigarette smoking increases the risk for the development and maintenance of PD. The carbon dioxide (CO2) challenge is well established as experimental model for panic. The present study seeks to examine whether cigarette smoking has an influence on laboratory elicited panic in PD patients.

Methods

In total 92 subjects (46 smokers and 46 non-smokers) with PD, according to the DSM-IV criteria, were compared. All subjects received a baseline clinical assessment and underwent a 35% CO2 challenge. Response to the challenge was evaluated via the Panic Symptom List and the Visual Analogue Fear Scale.

Results

The two samples did not differ on baseline anxiety level. Smokers had a significantly higher increase in panic symptoms in response to the challenge compared to non-smokers ($p = 0.04$). Limitations: This type of study does not provide information concerning the underlying mechanisms of the link between smoking and panic. Study limitations include lack of formal assessment of personality and of inter-rater reliability.

Conclusions

The present findings are consistent with the idea that smoking facilitates panic in PD subjects. This may have clinical implications, as quitting smoking could become one of the relevant steps in the treatment of PD patients.

Key words : Smoking, Panic Disorder, Carbon dioxide, Challenge

1. Introduction

A disproportionate number of people with panic disorder (PD) smoke cigarettes compared to those in the general population and to individuals with other anxiety disorders (Breslau et al.,1991; Amering et al., 1999; Johnson et al., 2000). Panic has been strongly associated with occasional smoking, regular smoking and nicotine dependence (Isensee et al., 2003; Breslau et al., 2004) according to a bidirectional pattern of association going from smoking to panic and from panic to smoking (Isensee et al., 2003).

Clinical and epidemiological data suggest that cigarette smoking increases the risk of developing certain anxiety disorders, in particular PD (Morissette et al., 2006). Longitudinal studies, in both adults and adolescents, have shown that daily smoking is related to an increased risk of initial occurrence of panic attacks (PAs) and PD (Breslau and Klein, 1999; Johnson et al., 2000).

Several explanations have been proposed for this relationship.

The first hypothesis posits an anxiogenic effect of nicotinecon-sumption and conceptualizes smoking as a risk factor for panic ('from smoking to panic') (Klein, 1993; Breslau and Klein, 1999; Pine et al., 2000; Caldirola et al., 2004; Zvolensky et al., 2004; Esquivel et al., in press).

The second hypothesis implies an anxiolytic effect of nicotine ('from panic to smoking') (Pohl et al., 1992; Kassel and Shiffman, 1997).

Finally, a shared vulnerability (genetic or environmental) may also explain this co-occurrence (Goodwin and Hamilton, 2002).

The majority of these studies however have been conducted in naturalistic settings, allowing no conclusion regarding the direction of this relationship. Laboratory based tests can be a useful additional research step in this respect.

In recent years, experimental psychiatry has developed different paradigms to provoke panic in an experimental setting. Experimental studies using laboratory panic provocation procedures focus on the underlying mechanisms of the panic/smoking link. The 35% CO2 inhalation method has proven to be a specific, valid, reliable, and safe way to induce experimental panic (Griez and Schruers, 1998; Esquivel et al., in press).

Previous experimental studies using the voluntary hyperventilation pro-cedure (Zvolensky et al., 2004) and the 4- minute 5% CO2 rebreathing challenge (Abrams et al., 2008) have shown that smokers react more on measures of fear, anxiety or distress. Cosci et al. (2006) however, comparing healthy smoking and non-smoking volunteers, found no difference on the response to the 35% CO2 challenge.

Considering the heterogeneity of methods in experimental studies and the fact that the temporal pattern, in epidemiological studies, is still a matter of debate, we designed a study to examine whether cigarette smoking has an influence on laboratory elicited panic in panic disor-der patients. We administered 35% CO2 challenge to regular smokers with PD and compared them to non-smokers with PD.

We hypothesize that cigarette smoking facilitates the emergence of panic ('from smoking to panic') and therefore expect smokers to respond stronger to the 35% CO2 challenge compared to PD non-smokers.

2. Methods

2.1. Subjects

The sample consisted of 92 outpatients with panic disorder; 46 smokers and 46 non-smokers (22 men in each group).

Participants were recruited from our outpatient setting. All participants were screened by an experienced psychiatrist. They had a medical history inventory, a psychiatric evaluation to confirm the diagnosis according to the DSM-IV criteria (APA, 1994) and an evaluation through the Mini International Neuropsychiatric Interview (Sheehan et al., 1994) to support the diagnoses.

Only patients with PD as primary diagnosis were included. Exclusion criteria: cardiovascular/ pulmonary disease, significant hypertension, pregnancy, epilepsy, cerebral aneurysm, use of concurrent psycho-tropic medication and adrenergic receptor blockers. None of the patients had been on diazepam or fluoxetine that requires a longer wash-out period. Patients with concurrent psychiatric disorders, according to the DSM- IV criteria (APA, 1994) were not excluded: in the smokers group one patient had a social phobia, one patient had a somatoform disorder, one patient had a dysthymic disorder and three had major depressive disorder.

In the non-smokers group there was one patient with generalized anxiety disorder, two with social phobia, one with somatoform disorder and three with major depressive disorder.

No formal assessment of personality was made.

The study was approved by the local medical ethics committee and all patients gave their informed consent after a detailed explanation of the entire procedure.

2.2. Procedures

All patients had a complete medical history and a psychiatric evaluation performed by an experienced psychiatrist. They were evaluated about smoking habits. Age of onset of smoking was defined as the age at which they started to smoke daily for at least 4 weeks (Breslau and Klein, 1999; Isensee et al., 2003). The amount of cigarettes smoked daily was also assessed. Current smokers had to use tobacco on daily basis for a period of at least 4 weeks continuously

(Breslau and Klein, 1999; Isensee et al., 2003). Non-smokers were defined as those who never used tobacco products.

Before the 35% CO2 inhalation procedure, clinical assessment of anxiety was performed by using three scales. The State–Trait Anxiety Inventory—State version (STAI-S) is a self-administered scale to assess momentary anxiety (Spiel- berger et al., 1970). The State–Trait Anxiety Inventory—Trait version (STAI-T) is a self-administered scale to assess general anxiety (Spielberger et al., 1970). The Fear Questionnaire (FQ) is a self-rating scale which assesses agoraphobia, blood-injury phobia and social phobia. It produces a global score (FQ-tot) and subscores for agoraphobia (FQ-AGO), blood-injury phobia (FQ-BI) and social phobia (FQ-SOC) (Marks and Mathews, 1979).

Before and after the 35% CO2 inhalation, physiological and psychological symptoms were assessed using a Visual Analogue Scale of Fear (VAS-F) and the Panic Symptom List (PSL) which have been regularly used to assess experimental

anxiety (Perna et al., 1995; Schruers et al., 2000). The procedure of the 35% CO2 challenge has been described elsewhere (Schruers and Griez, 2004). An increase in at least four physical symptoms of the PSL together with an increase of at least 25 units in the VAS-F were used as criteria for an experimental panic attack.

2.3. Data analysis

Chi square test was used for categorical variables (gender, occurrence of CO2 challenge induced panic attack). For non- categorical data with a normal distribution Student's t-test was used (age, FQ Total, FQ-AGO, STAI-S, STAI-T, VAS-F, PSL). The results are presented as means ± standard deviations and significance levels were set at $p < 0.05$ (two-tailed). The main outcome measures were the delta VAS-F and delta PSL. Deltas are calculated as 35% CO2 post-challenge minus 35% CO2 pre- challenge scores.

3. Results

Ninety-two patients (46 smokers and 46 non-smokers) with a diagnosis of panic disorder were evaluated (Agoraphobia was diagnosed in about 76% of the patients). There was no significant difference between both groups concerning gender (24 of the smokers and 24 of the non-smokers were female) or age (33.9 ± 10.6 in smokers and 35.7 ± 12 in non-smokers; $p = 0.46$).

Among smokers, the mean daily consumption of cigarettes was 14.8 ± 8.9 (n = 42). Fifty percent (n =23) smoked 1–10 cigarettes per day, 39% (n = 18) smoked 11–20 cigarettes per day, 6% (n =3) smoked 21–30 cigarettes per day and 4% (n =2) smoked more than 30 cigarettes per day.

The two samples did not differ regarding avoidance behavior or level of anxiety as evaluated at baseline by means of the FQ Total, FQ-AGO, STAI-S and STAI-T (Table 1). Smokers and non-smokers did also not significantly differ for VAS-F and PSL pre-challenge scores (Pre-VAS-F: 25.3 ± 21.3 in smokers and 28.6 ± 24.5 in non-smokers; $p = 0.49$. Pre-PSL: 4.1 ± 4.6 in smokers and 4.6 ± 4.3 in non-smokers; $p = 0.55$), for VAS-F and PSL post-challenge scores (Post-VAS-F: 69.1 ± 22.3 in smokers and 65.2 ± 24.8 in non-smokers; $p = 0.4$. Post-PSL: 17 ± 9.2 in smokers and 14.3 ± 7.3 in non-smokers; $p = 0.12$) or for delta VAS-F (43.8 ± 23.8 in smokers and 36.3 ± 23.6 in non-smokers; $p = 0.13$). However, smokers had lower VAS-F and PSL scores immediately before the challenge and reached higher scores immediately after (Figs. 1 and 2). The delta PSL scores revealed a significant difference between the smokers and non-smokers with smokers displaying a stronger reaction (12.9 ± 8.3 in smokers and 9.7 ± 6.7 in non-smokers; $p = 0.04$). Finally, smokers and non-smokers did not differ as for number of 35% CO2 induced panic attacks. 65% (30/46) of smokers versus 56% (26/46) of non-smokers ($p = 0.39$).

4. Discussion

The present study shows that PD smokers responded stronger to a 35% CO2 panic challenge compared to PD non-smokers. PD smokers reacted with more panic symptoms to the challenge while baseline measures were similar in both groups.

Fear scores showed the same effect, however without reaching statistical significance as has been the case in previous studies (Cosci et al., 2004, 2005). The findings fit the hypothesis that prior regular smoking increases the risk for panic attacks in PD patients.

Table1. Comparison of PD smokers and PD non-smokers on clinical characteristics and severity of panic disorder as assesses at baseline

	Smokers			**Non-smokers**			**p**
	N	**Mean**	**SD**	**N**	**Mean**	**SD**	
STAI-S	42	45.3	13.0	42	46.4	13.3	0.69
STAI-T	18	47.4	13.6	16	44.0	11.6	0.45
FQ Total	41	39.1	23.2	40	37.0	25.3	0.70
FQ-AGO	41	15.2	11.8	41	12.6	13.2	0.35

Student's t-test for independent samples.

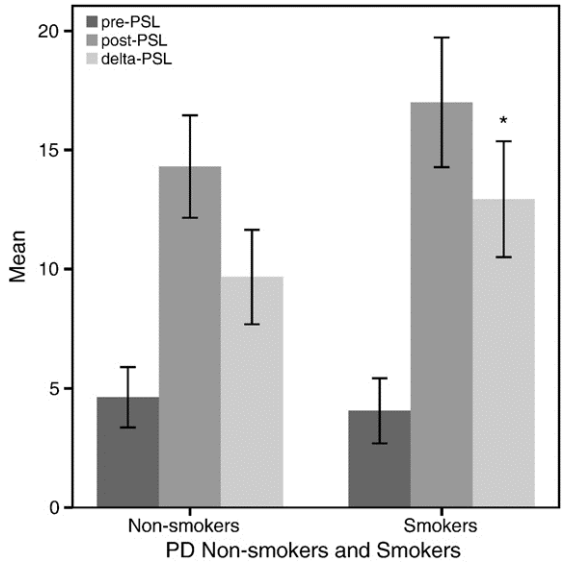

Fig. 1. Comparison of PD smokers with PD non-smokers concerning pre- and post-challenge assessment with PSL. Student's t-test for independent samples. $*p < 0.05$, two-tailed. Error bars: +/−2 SE.

A previous study in our laboratory was aimed at testing whether nicotine has a direct influence on laboratory-elicited panic (Cosci et al., 2006). We compared healthy non-smokers undergoing a 35% CO2 challenge after a transdermal admin istration of a nicotine or placebo patch, according to a cross- over design. Nicotine did not significantly affect the reaction to the 35% CO2 challenge compared to placebo. At first sight, these previous results don't seem to agree with the present

study. Yet, lack of response to the 35% CO2 challenge itself, may have several explanations.

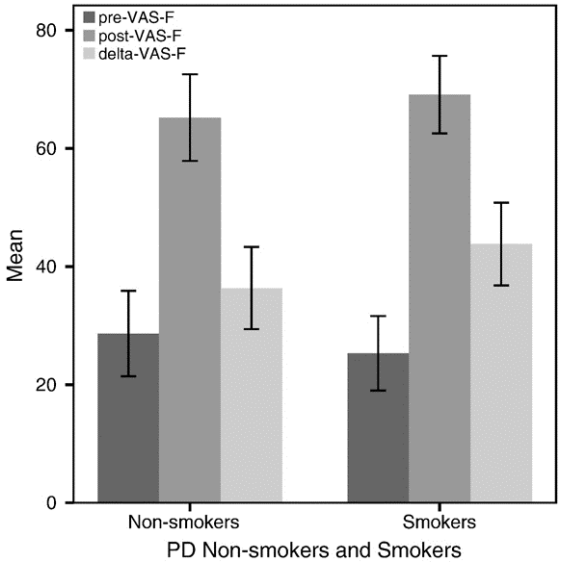

Fig. 2. Comparison of PD smokers with PD non-smokers concerning pre- and post-challenge assessment with VAS-F. Students t-test for independent samples. Error bars : +/- 2 SE.

First of all, in the previous study nicotine was administered acutely, while in the present study cigarette smoking was used as a proxy of chronic exposure to nicotine. In real life, smokers are also chronically or sub-acutely exposed to nicotine and this may imply a different pharmacological effect (De Graaf et al.,2002; Isensee et al., 2003). It is conceivable that a longer exposure to nicotine is more likely to cause increased sensitivity to the challenge, as demonstrated in the present study.

Second, the previous study was carried out in healthy volunteers, not in PD patients. Recent results from our group showed that while a single 35% CO2 inhalation is capable of provoking panic in PD patients, this stimulus is not sufficiently strong in most healthy volunteers (Griez et al., 2007).

Third, in the previous study nicotine was administered via nicotine patches. It can be argued that using cigarette smoking as a proxy of chronic exposure to nicotine may introduce a bias, as it is well known that tobacco includes, besides the nicotine, more than four thousand different constituents (Burns, 1991). Nevertheless, the effect of cigarette smoking on the central nervous system has been mainly attributed to the pharmacological action of nicotine (Dilsaver, 1987).

Fourth, in the previous study all subjects were non-smokers and a comparison was made between subjects who received nicotine versus placebo via patches. In the present study smokers and non-smokers were compared. It might be that regular smoking, may increase the risk of an overreaction to suffocation signals and

therefore increase the risk for panic (Breslau and Klein, 1999; Pine et al., 2000; Caldirola et al., 2004).

The results of the present study are in line with other experimental studies. Zvolensky et al. (2004) evaluated anxious and fearful responding to bodily sensations as a function of panic disorder and smoking status. Participants completed a voluntary hyperventilation procedure that elicits panic-relevant bodily sensations. At the pre-challenge assessment, smokers with PD did not differ from non-smokers with PD on baseline anxiety. At the post-challenge assessment, smokers with PD reported greater levels of anxiety and bodily distress than non- smokers with PD. In our study smokers and non-smokers had also similar baseline anxiety scores, both on STAI and FQ scales. Lack of difference in the pre-challenge state anxiety between smokers with PD and non-smokers with PD rules out that smokers were more fearful following the challenge because of a higher baseline fear. Abrams et al. (2008) examined 24 adult heavy smokers in 12-h nicotine withdrawal and 24 adult non- smokers on subjective and physiological reactivity to a 4-min carbon dioxide rebreathing challenge. Results indicated that smokers experienced a significantly greater increase in self- reported panic symptoms than non-smokers.

Study limitations include lack of formal assessment of personality and of interrater reliability.

In conclusion, the present findings are consistent with previous research that cigarette smoking appears to have the capacity to serve as a causal factor/facilitator in the development of PD. Cigarette smoking tends to precede the onset of panic and to promote panic itself, however the temporal pattern and the etiopathogenetic explanations of such a co-occurrence are still being discussed.

Our results may have clinical implications, as smoking ces- sation might be a strategy in the prevention of panic (disorder) and could also be part of treatment strategy in PD.

References

Abrams, K., Zvolensky, M., Dorflinger, L., Galatis, A., Blank, M., Eissenberg, T., 2008. Fear reactivity to bodily sensations among heavy smokers and non-smokers. Exp. Clin. Psychopharmacol. 16 (3), 230–239.

American Psychiatric Association (APA), 1994. Diagnostic and Statistical Manual of Mental Disorders. Washington DC.

Amering, M., Bankier, B., Berger, P., Griengl, H., Windhaber, J., Katschnig, H., 1999. Panic disorder and cigarette smoking behaviour. Compr. Psychiatry 40, 35–38.

Breslau, N., Klein, D.F., 1999. Smoking and panic attacks: an epidemiologic investigation. Arch. Gen. Psychiatry 56 (12), 1141–1147.

Breslau, N., Kilbey, M., Andresti, P., 1991. Nicotine dependence, major depression, and anxiety in young adults. Arch. Gen. Psychiatry 48 (12), 1069–1074.

Breslau, N., Novak, S.P., Kessler, R.C., 2004. Daily smoking and the subsequent onset of psychiatric disorders. Psychol. Med. 34 (2), 323–333.

Burns, D.M., 1991. Cigarettes and cigarette smoking. Clin. Chest Med. 12 (4), 631–642.

Caldirola, D., Bellodi, L., Cammino, S., Perna, G., 2004. Smoking and respiratory irregularity in panic disorder. Biol. Psychiatry 56, 393–398.

Cosci, F., Schreurs, K., Faravelli, C., Griez, E. (2004). The influence of alcohol oral intake on the effects 35% CO2 challenge. A study in healthy volunteers. Acta Neuropsychiatr. 16 (2), 107–109.

Cosci, F., De Gooyer, T., Schruers, K., Favarelli, C., Griez, E.J.L., 2005. The influence of ethanol infusion on the effects of 35% CO2 challenge. A study in panic disorder patients and healthy volunteers. Eur. Psychiatry 20, 299–303.

Cosci, F., Abrams, K., Schruers, K.R., Rickelt, J., Griez, E.J., 2006. Effect of nicotine on 35% CO2-induced anxiety: a study in healthy volunteers. Nicotine Tob. Res. 8 (4), 511–517.

De Graaf, R., Bijl, R.V., Smit, F., Volebergh, W.A., Spijker, J., 2002. Risk factors for 12-month comorbidity of mood, anxiety, and substance use disorders: findings from The Netherlands mental health survey and incidence study. Am. J. Psychiatry 159, 620–629.

Dilsaver, S.C., 1987. Nicotine and panic attacks. Am. J.Psychiatry 144, 1245–1246.

Esquivel, G., Schruers, K., Maddock, R.J., Colasanti, A., Griez, E., in press. Acids in the brain. A factor in panic? J. Psychopharmacol. (May 21, 2009)Electronic publication ahead of print). doi:10.1177/0269881109104847.

Goodwin, R., Hamilton, S.P., 2002. Cigarette smoking and panic: the role of neuroticism. Am. J. Psychiatry 159 (7), 1208–1213.

Griez, E., Schruers, K., 1998. Experimental pathophysiology of panic. J. Psychosom. Res. 45 (6), 493–503.

Griez, E.J., Colasanti, A., van Diest, R., Salamon, E., Schruers, K., 2007. Carbon dioxide inhalation induces dose-dependent and age-related negative affectivity. PloS ONE 2 (10), e987.

Isensee, B., Wittchen, H.U., Stein, M.B., Höfler, M., Lieb, R., 2003. Smoking increases the risk of panic: findings from a prospective community study. Arch. Gen. Psychiatry 60 (7), 692–700.

Johnson, J.G., Cohen, P., Pine, D.S., Klein, D.F., Kasen, S., Brook, J.S., 2000. Association between cigarette smoking and anxiety disorder during adolescence and early adulthood. JAMA 284, 2348–2351.

Kassel, J.D., Shiffman, S., 1997. Attentional mediation of cigarette smoking's effect on anxiety. Health Psychol. 16, 359–368.

Klein, D.F., 1993. False suffocation alarms, spontaneous panics, and related conditions: an integrative hypothesis. Arch. Gen. Psychiatry 50, 306–317.

Marks, I.M., Mathews, A.M., 1979. Brief standard self-rating for phobic patients. Behav. Red. Ther. 17 (3), 263–267.

Morissette, S.B., Brown, T.A., Kamholz, B.W., Gulliver, S.B., 2006. Differences between smokers and nonsmokers with anxiety disorders. J. Anxiety Disord. 20 (5), 597–613.

Perna, G., Barbini, B., Cocchi, S., Bertani, A., Gasperini, M., 1995. 35% CO2 challenge in panic disorders. J. Affect. Disord. 33, 189–194.

Pine, D.S., Klein, R.G., Coplan, J.D., Papp, L.A., Hoven, C.W., Martinez, J., Kovalenko, P., Mandell, D.J., Moreau, D., Klein, D., Gorman, J.M., 2000. Differential carbon

dioxide sensitivity in childhood anxiety disorders and non ill comparison group. Arch. Gen. Psychiatry 57 (10), 960–967.

Pohl, R., Yeragani, V.K., Balon, R., Lycaki, H., McBride, R., 1992. Smoking in patients with panic disorder. Psychiatry Res. 43, 253–262.

Schruers, K., Griez, E., 2004. The effects of tianeptine or paroxetine on 35% CO2 provoked panic in panic disorder. J. Psychopharmacol. 18 (4), 553–558.

Schruers, K., Pols, H., Overbeek, T., Griez, E., 2000. 10 microg CCK-4 premedication and 35% CO2 challenge in healthy volunteers. Prog. Neuropsychopharmacol. Biol. Psychiatry 24 (3), 409–418.

Sheehan, D., Lecrubier, Y., Janavs, J., Knapp, E., Weiller, E., 1994. MINI International Neuropsychiatric Interview. University of South Florida, Tampa.

Spielberger, C.D., Gorsuch, R., Lushene, R.N., 1970. Manual for the State–Trait Anxiety Inventory. Consulting Psychologists Press, Palo Alto, Calif.

Zvolensky, M.J., Leen-Feldner, E.W., Feldner, M.T., 2004. Emotional responding to biological challenge as a function of panic disorder and smoking. J. Anxiety Disord. 18 (1), 19–32.

Chapter four

Cigarette Smoking and Panic: A Critical Review of the Literature

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Abstract

Objective

Cigarette smoking increases the risk of panic disorder with or without agoraphobia's emerging. Although the cause of this comorbidity remains controversial, the main explanations are that (1) cigarette smoking promotes panic by inducing respiratory abnormalities/lung disease or by increasing potentially fear-producing bodily sensations, (2) nicotine produces physiologic effects characteristic of panic by releasing nor-epinephrine, (3) panic disorder promotes cigarette smoking as self-medication, and (4) a shared vulnerability promotes both conditions. The aim of this review was to survey the literature in order to determine the validity of these explanatory models.

Data sources

Studies were identified by searching English language articles published from 1960 to November 27, 2008, in MEDLINE using the keywords: nicotine AND panic, tobacco AND panic,and smoking AND panic.

Study selection

Twenty-four studies were reviewed and selected according to the following criteria: panic disorder with or without agoraphobia and nicotine dependence, when used, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, Fourth Edition, or Fourth Edition, Text Revision; no additional comorbidity or, if present, adjustment for it in the statistical analyses; use of adult or adolescent samples; comparison with a nonclinical control group or application of a crossover design.

Data extraction

Non-significant results or trends only were reported as no difference. Data on anxiety disorders or substance abuse in general were not included.

Data synthesis

Panic and cigarette smoking each appear to have the capacity to serve as a causal factor/facilitator in the development of the other. Although the temporal pattern and the pathogenetic explanations of such a co-occurrence are still being discussed, cigarette smoking tends to precede the onset of panic and to promote panic itself.

Conclusions

Additional studies are strongly recommended.

Inroduction

A disproportionate number of people with panic, in the form of either panic attacks or panic disorder, smoke cigarettes compared to those in the general population[1,2] and to individuals with other anxiety disorders.[3] The temporal pattern underlying such a co-occurrence is still a matter of debate. Indeed, although panic can been associated with smoking and nicotine dependence [4–8] according to a bidirectional temporal pattern (going from smoking to panic or from panic to smoking),[7] clinical and experimental data have suggested that cigarette smoking increases the risk of panic disorder's emerging.[9] Similarly, longitudinal studies [3–10] have supported the more common pattern of primary smoking and secondary panic occurrence.

Several explanations have been proposed for this relationship: (1) cigarette smoking may lead to the onset of panic by inducing respiratory abnormalities [11–13] or lung disease. Thus, smoking may increase the risk of panic because, according to the false suffocation alarm theory,[10,14] it induces an overreaction to suffocation signals; (2) nicotine may produce physiologic effects characteristic of panic attacks by promoting the release of norepinephrine into the brainstem [15]; (3) smoking may modify the expression of panic disorder by increasing potentially fear-producing bodily sensations.[16] Thus, individuals with panic disorder who usually perceive themselves as being physically unhealthy would more likely react with exaggerated anxiety.

A different, less frequent, reverse pathway of primary panic and secondary nicotine dependence cannot be excluded.[7] One hypothesis for this pathway is that panic disorder patients smoke as a means of self-medicating their symptoms, [1,17] because of the anxiolytic (pharmacologic) effects of nicotine [18] or because of cognitive mechanisms (smoking narrows the focus of attention and diverts one from stressful cognitions).[19]

A shared vulnerability has been also advanced suggesting that personality, and in particular neuroticism, may be responsible for such a co-occurrence. [20]

Finally, according to Berkson's bias (ie, a type of selection bias that may occur in case-control studies when controls are selected within the hospital instead of from the general population), the illusion of relationship due to an overrepresentation of patients with both disorders can be hypothesized. However, this potential for bias applies only to clinical studies and not to those conducted in community samples.

Since matters may not be that clear-cut, the present article reviews the existing data on comorbidity between cigarette smoking/nicotine dependence and panic (either panic attacks or panic disorder with or without agoraphobia). The aim is to get a broader perspective on the relationship between panic and cigarette smoking and to identify the possible underlying etiologic mechanisms.

Method

A computerized search was carried out (PUBMED1960–2008) using the key words nicotine AND panic, tobacco AND panic, and smoking AND panic. In addition, the reference lists from existing reviews and from the articles retrieved were inspected. Only English language articles published in peer-reviewed journals were included.

We included studies in the general population, in panic disorder with or without agoraphobia/panic attacks patients, and studies adopting experimental models for panic disorder, as these latter are particularly suited to elucidate possible underlying mechanisms of the co-occurrence between smoking and panic.

In epidemiologic surveys, statistical analyses had to be adjusted for comorbid psychiatric disorders different from nicotine dependence, if present.

In the general and clinical population studies, the diagnosis of panic disorder with or without agoraphobia had to be made according to the Diagnostic and Statistical Manual of Mental Disorders Third Edition, Revised (DSM-III-R),[21] Fourth Edition (DSM-IV),[22] or Fourth Edition, Text Revision (DSM-IV-TR).[23] The definition of panic attacks had to conform to those proposed by the DSM-III-R, DSM-IV, or DSM-IV-TR.

A control group or a crossover design was required, except in epidemiologic surveys.

Studies were excluded when the data referred to anxiety disorders or substance use disorders in general.

In order to work with the most conservative approach possible, non-significant results or trends were reported as no difference.

Results

Twenty-four studies, of the 61 screened, met our inclusion criteria. First, we present an overview of studies estimating the prevalence of the co-occurrence of cigarette smoking/ nicotine dependence and panic attacks/panic disorder with or without agoraphobia. Second, we offer an overview of studies that examined the 3 causal models (from panic to smoking, from smoking to panic, and shared vulnerability) in turn. Finally, experimental studies using laboratory panic provocation procedures will be considered. These studies focus on the underlying mechanisms of the panic/smoking link.

To assist the reader, we report, in Table 1, the samples under study and the definitions of smoking status used and, in Table 2, the parameters measured and the primary results obtained in the studies included in the present review.

Co-Occurrence of Panic and Smoking

In an epidemiologic survey,[24] the lifetime frequency of panic disorder was higher among smokers than nonsmokers for women, while no difference was found for men. Moreover, in a subsample of the National Comorbidity Survey (NCS),[25,26] current and lifetime smokers had significantly higher rates of panic disorder with or without agoraphobia than respondents from the general population, when either lifetime or past-month occurrence was evaluated. Thus, subjects exposed to smoking, either currently or throughout their lifetimes, are at a higher risk of experiencing panic than the general population.

Studies conducted in clinical samples seem to confirm such a co-occurrence. Zvolensky et al[16] found that smokers who had panic disorder with or without agoraphobia reported a higher level of anxiety than nonsmokers who had panic disorder with or without agoraphobia. The authors proposed that smoking modifies the expression of panic disorder with or without agoraphobia by promoting more

severe emotional disturbances. Indeed, smoking may confer a negative effect for specific anxiety-related symptoms, enhancing anxiety symptoms and worry about them. From this perspective, Zvolensky and coworkers suggested that smokers with panic disorder would not be more likely to have panic attacks than nonsmokers with panic disorder but would experience more frequent anxiety symptoms.

Four studies have compared the specificity of smoking and panic disorder versus other anxiety disorders. In a national household survey in Great Britain,[27] the prevalence of panic disorder in the nicotine-dependent population was significantly higher than in the nonnicotine–dependent population. Similar results were found for generalized anxiety and phobias.

With regard to the clinical samples, the prevalence of cigarette smoking was investigated in 5 groups of outpatients (ie, depressive disorder, panic disorder, social anxiety disorder, other anxiety disorders, and comorbidity disorders).[28] No significant differences were found.

McCabe et al[29] found different results when examining smoking behaviors among patients who had panic disorder with or without agoraphobia, social phobia, and obsessive-compulsive disorder (OCD). A significantly greater proportion of the panic disorder with or without agoraphobia group reported being a current smoker or a heavy smoker than the social phobia group and the OCD group.

Finally, Goodwin and coworkers[30] investigated the association between mental disorders and nicotine dependence among pregnant women. With regard to anxiety disorders, nicotine dependence significantly predicted the occurrence of panic disorder with or without agoraphobia, social phobia, specific phobia, and generalized anxiety disorder. However, after adjustments for demographic differences and comorbid Axis I and Axis II mental disorders were made, the only association that remained significant was between nicotine dependence and panic disorder with or without agoraphobia.

In brief, a specific relationship between panic disorder with or without agora-phobia (vs other anxiety disorders) and cigarette smoking/nicotine dependence seems to be still a matter of debate. Only 2 studies of the 4 described above supported a unique relationship between panic disorder with or without agora-phobia and cigarette smoking/ nicotine dependence.

From Panic to Smoking

Isensee and coworkers7 prospectively evaluated adolescents and young adults. This is, to our knowledge, the only study showing that subjects with pre-existing baseline panic attacks or panic disorder have an increased risk for onset of nicotine dependence.

From Smoking to Panic

Breslau and coworkers1 evaluated a random sample of young adults and found that nicotine-dependent smokers are at a higher risk of developing panic than nonsmokers. Moreover, the higher the level of nicotine dependence, the higher the risk of panic.

When the NCS[23] and the Epidemiologic Study of Young Adults datasets[10] were analyzed, a significantly higher risk of panic occurrence (either panic attacks or panic disorder) was found in subjects with pre-existing smoking if compared to

nonsmokers and in subjects who persist in smoking after panic onset compared to nonsmokers.

Examining subjects with a history of panic and a history of daily smoking, Bernstein et al[31] found that the earlier the age at onset of daily smoking, the greater the risk of developing panic disorder.

Longitudinal studies have found similar results. In one study, adolescents who smoked 20 cigarettes or more per day were at elevated risk of panic disorder with agoraphobia during both adolescence and early adulthood when compared with those who smoked fewer than 20 cigarettes per day.[3]

Nondependent regular smokers and dependent smokers were at higher risk of panic attacks than nonsmokers, and an elevated risk was maintained in dependent smokers when compared to occasional smokers.[7]

Current smokers, with or without nicotine dependence, were at higher risk of panic disorder occurrence than non- smokers, while being a former smoker seemed to reduce such a risk. Examining the relationship between time elapsed since quitting and the risk of the first onset of panic disorder in past daily smokers, using a standardized variable that counts the number of years passed beginning with the year after quitting, researchers found that the likelihood of panic was reduced by one-half with each standard deviation unit of time elapsed since quitting.[8] Thus, the authors showed some evidence that smoking cessation might reduce the risk of subsequent panic.

Some hypotheses explaining the co-occurrence of smoking and panic have been proposed. Breslau and Klein[10] suggested that lung disease might be one of the mechanisms linking smoking to panic. By increasing the risk of lung disease, smoking might indirectly increase the risk of panic attacks. In addition, they found that, according to the false suffocation alarm theory,[14] cigarette smoking, by leading to chronic bronchitis and emphysema as well as to subclinical respiratory impairment, may favor panic attacks in subjects predisposed to overreaction to suffocation signals. Alternatively, they proposed that the carbon monoxide in cigarette smoke might affect the suffocation alarm threshold via inhibition of the carotid body.[32]

Another interesting hypothesis was put forth by Leen-Feldner et al.[33] Observing that smoking status was related to elevations in panic frequency among adolescents who were high in health fear, they suggested that, if a smoker experiences disease or illness, she or he may develop health fear, and exposure to smoke may increase attention to, and catastrophic misinterpretation of, bodily cues. Over time, the repeated pairing of fear with bodily cues may result in a learned association, such that somatic events ultimately elicit a panic-type response.

Table 1. Study Populations and Definitions of Smoking Status in Studies of Cigarette Smoking and Panic Selected for Review

Study	Study Population	Definition of Smoking Status
Black et al[24]	First-degree relatives of psychiatric patients (n = 697) and normal controls (n = 360)	Nonsmoker = never smoked; smoker = all others
Lasser et al[25]	General population (n = 4,411)	Current smoker = smoked in the past month; lifetime smoker = smoked daily for at least 1 month
Zvolensky et al[16]	PD(A) patients (n = 140)	Smoker = smoked > 10 cigarettes/d; nonsmoker = smoked 0 cigarettes/d
Farrell M et al[27]	General population (n = 10,018)	Nicotine dependent = according to the *ICD-10*[44]
Lopes et al[28]	Outpatients (n = 262) and controls (n = 68)	Regular smoker = smoked for at least 4 weeks and still smoking at the time of the interview; exposed subject = smoked in lifetime; nonsmoker = all others
McCabe et al[29]	PD(A), social phobia, and OCD (n = 155)	Current smoker = consumed at least 1 cigarette/d for at least 6 months; past smoker = smoked in the past and was abstinent for at least the last 3 months
Goodwin et al[30]	Pregnant women reporting pregnancy in the past year (n = 1,516)	Nicotine dependent = according to the *DSM-IV*
Isensee et al[7]	General population (n = 3,021)	Nonsmoker = never used tobacco products lifetime; occasional smoker = used at least 1 tobacco product in lifetime but never on a daily basis for a period of at least 4 weeks; nondependent regular smoker = smoked cigarettes daily for at least 4 weeks but never met *DSM-IV* criteria for nicotine dependence, dependent regular smoker = smoked cigarettes daily for a period of at least 4 weeks and met *DSM-IV* criteria for nicotine dependence
Breslau et al[1]	General population (n = 1,007)	Nicotine dependent = according to the *DSM III-R*
Breslau et al[10]	General population (n = 4,411 in one sample; n = 1,007 in the other sample)	Daily smoker = smoked daily for 1 month or longer
Bernstein et al[31]	General population (n = 4,409)	Lifetime regular smoker = smoked in lifetime for at least 1 month; current regular smoker = smoked for at least the past month
Johnson et al[3]	General population (n = 688)	Sample stratified using a cutoff of 1 pack of cigarettes smoked/d during adolescence (< 1 pack/d n = 649; ≥ 1 pack/d n = 39)
Breslau et al[8]	General population (n = 4,411)	Pre-existing daily smoker = smoked 1 year or more before the year of onset of PD; past smoker = smoked 1 year or more before the onset of PD; current smoker = continued to smoke in the year of the onset of the disorder
Leen-Feldner et al[33]	General population (n = 249)	Current smoker = smoked in the previous 30 days
Pohl et al[17]	217 patients with PD(A) and 217 age- and sex-matched controls	Smoker = has used cigarettes daily regularly
Amering et al[2]	PD patients (n = 102)	Assessment of smoking status at the onset of panic: onset, duration, daily number of cigarettes, and changes in cigarette consumption over time
Reichborn-Kjennerud et al[34]	Female-female twin sample (n = 3,172)	Lifetime daily smoker = has used cigarettes daily regularly
Agrawal et al[35]	Monozygotic and dizygotic twin pairs, including opposite sex twins (n = 6,257)	Regular cigarette smoker = has smoked between 20 and 100 times in lifetime and as often as 1 or 2 days a week (or daily) for a period of 3 weeks or longer
Goodwin et al[36]	General population (n = 940)	Daily lifetime smoker and ever lifetime smoker on the basis of lifetime cigarette use, current frequency of cigarette smoking, and highest previous frequency of cigarette smoking
Zvolensky et al[37]	General population (n = 924)	Current regular smoker = has regularly self-reported smoking during the past month
Brooks et al[38]	17 PD(A) smokers and 22 PD(A) nonsmokers matched for age and sex	Nonsmoker = has been abstinent for at least 2 years; smoker = has had a regular habit of smoking more than 10 cigarettes/d for at least 6 months
Zvolensky et al[39]	Who regularly daily has used cigarettes PD regular smokers, 20 PD nonsmokers, 20 regular smokers without PD	Regular smoker = has smoked at least 10 cigarettes/d
Cosci et al[42]	Healthy nonsmokers (n = 33)	Nonsmoker = has smoked fewer than 10 cigarettes in lifetime and none in the last 5 years
Abrams et al[43]	24 heavy smokers in 12-hour nicotine withdrawal and 24 nonsmokers	Smoker = has smoked at least 20 cigarettes/d for at least 2 years, was nicotine dependent as indicated by a score of 5 or greater on the Fagerstrom Test of Nicotine Dependence, and has not attempted to cut back or quit smoking in the previous month; nonsmoker = has used fewer than 10 nicotine products in lifetime and none in the past 5 years

Abbreviations: *DSM-III-R* = *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised, *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, ICD-10 = *International Statistical Classification of Diseases and Related Health Problems,* Tenth Revision, PD = panic disorder, PD(A) = panic disorder with or without agoraphobia.

Table 2. Parameters Measured and Primary Results in Studies of Cigarette Smoking and Panic Selected for Review

Study	Parameters Measured	Primary Results
Black et al[24]	Lifetime prevalence of PD smokers vs nonsmokers	Women: 5.6% vs 2.1%; OR = 2.8; 95% CI, 1.1–7.0
Lasser et al[25]	Lifetime prevalence of PD current smokers vs US population	35.9% vs 3.4%, $P < .001$
	Lifetime smokers vs US population	61.3% vs 3.4%, $P \leq .0001$
	Prevalence of PD in the past month	
	Current smokers vs US population	42.6% vs 4%, $P < .001$
	Lifetime smokers vs US population	63.5% vs 4%, $P < .0001$
Zvolensky et al[16]	Comparison of means	
	PD(A) smokers vs PD(A) nonsmokers	Beck Anxiety Index: 22.54 ± 13.23 vs 33.06 ± 16.49, $P < .01$
		Sheehan Patient Rated Anxiety Scale: 51.97 ± 27.81 vs 71.63 ± 33.79, $P < .05$
		Panic Disorder Severity Scale anticipatory anxiety about panic: 2.19 ± 1.17 vs 3.00 ± 1.20, $P < .05$
		Panic Disorder Severity Scale composite: 1.94 ± 0.78 vs 2.39 ± 0.96, $P < .05$
		Disability Scale social: 4.66 ± 2.83 vs 6.31 ± 3.18, $P < .05$
		Panic Disorder Severity Scale social interference: 1.57 ± 1.18 vs 2.47 ± 1.36, $P < .01$
		Days for gastrointestinal illness: 0 vs 0.65, $P < .01$
		Days for cardiovascular illness: 0 vs 0.37, $P < .05$
Farrell et al[27]	Prevalence of different anxiety disorders	
	Nonnicotine dependents vs nicotine dependents	PD: 0.5% vs 1.5%, $P < .001$
		GAD: 2.4% vs 4.1%, $P < .001$
		Phobias: 0.8% vs 1.5%, $P < .001$
Lopes et al[28]	Prevalence of cigarette smoking	
	Depressive disorder vs PD vs social anxiety disorder vs other anxiety disorders vs comorbidity disorders	Difference NS
McCabe et al[29]	Prevalence of current cigarette smoking	
	PD(A) vs SP	40.4% vs 19.6%, $P < .05$
	PD(A) vs OCD	40.4% vs 22.4%, $P < .05$
	Prevalence of heavy cigarette smoking	
	PD(A) vs SP	30.8% vs 14.3%, $P < .05$
	PD(A) vs OCD	30.8% vs 10.2%, $P < .05$
Goodwin et al[30]	Prevalence of PD(A)	
	Nicotine dependents vs nonnicotine dependents	3.0% vs 0.4%; OR = 3.1; 95% CI, 1.58–6.09
Isensee et al[7]	Baseline association between smoking status and PAs	
	Occasional smokers vs nonsmokers	2.0% vs 0.7%; OR = 3.0; 95% CI, 1.2–7.1
	Nonnicotine dependents vs nonsmokers	1.9% vs 0.7%; OR = 3.0; 95% CI, 1.1–8.0
	Nicotine dependents vs nonsmokers	7.6% vs 0.7%; OR = 12.8; 95% CI, 5.6–28.9
	Baseline association between smoking status and PD	
	Occasional smokers vs nonsmokers	1.3% vs 0.2%; OR = 9.8; 95% CI, 1.2–74.7
	Nonnicotine dependents vs nonsmokers	2.1% vs 0.2%; OR = 13.8; 95% CI, 1.7–108.6
	Nicotine dependents vs nonsmokers	3.8% vs 0.2%; OR = 28.0; 95% CI, 3.7–208.4
	Association between smoking status at baseline and new onset of PAs	
	Nonnicotine dependents vs nonsmokers	3.6% vs 1.4%; OR = 2.9; 95% CI, 1.0–8.9
	Nicotine dependents vs nonsmokers	4.4% vs 1.4%; OR = 3.6; 95% CI, 1.2–10.5
	Nicotine dependents vs occasional smokers	4.4% vs 2.0%; OR = 2.4; 95% CI, 1.0–5.2
	Association between panic and the subsequent onset of nicotine dependence	
	Cox regression with time-dependent covariates	PAs: HR 3.3, 95% CI, 2.5–4.5
		PD: HR = 3.3; 95% CI, 2.1–5.1
	Association between pre-existing panic and the risk of subsequent onset of smoking	
	Cox regression with time-dependent covariates	HR = 2.7; 95% CI, 1.7–4.2
	Association between nicotine dependence and the risk of subsequent onset of PAs	
	Nicotine dependents vs nonsmokers	HR = 2.7; 95% CI, 1.7–4.2
Breslau et al[1]	Risk of PD occurrence	
	Moderately dependent vs nondependents	OR = 2.86; 95% CI, 1.04–7.90
Breslau and Klein[10]	NCS	NCS
	Risk of lifetime association of PAs	Men: OR = 1.64; 95% CI, 1.10–2.50
		Women: OR = 1.69; 95% CI, 1.26–2.25
	Daily smokers vs nonsmokers	HR = 2.02; 95% CI, 1.47–2.77
	Smokers who had quit	HR=1.85; (95% CI, 0.98–3.50
	Persistent smokers vs nonsmokers	HR = 2.07; 95% CI, 1.49–2.87
	Risk of lifetime association of PD	
	Daily smokers vs nonsmokers	OR = 1.60; 95% CI, 1.27–2.18
	Prior daily smokers vs nonsmokers	HR = 2.93; 95% CI, 1.84–4.66
	Persistent daily smokers vs nonsmokers	HR = 3.18; 95% CI, 1.99–5.10
	Epidemiologic Study of Young Adults	Epidemiologic Study of Young Adults
	Risk of lifetime association of PAs	Men: OR = 3.13; 95% CI, 1.30–7.50
		Women: OR = 2.61, 95% CI, 1.66–4.09
	Daily smokers vs nonsmokers	HR = 3.96; 95% CI, 2.28–6.89
	Smokers who had quit	HR=0.21; (95% CI, 0.05–0.88
	Persistent smokers vs nonsmokers	HR = 4.71; 95% CI, 2.70–8.21
	Risk of lifetime association of PD	
	Daily smokers vs nonsmokers	OR = 4.24; 95% CI, 2.23–8.06
	Prior daily smokers vs nonsmokers	HR = 13.13; 95% CI, 4.41–39.10
	Persistent smokers vs nonsmokers	HR = 14.46; 95% CI, 4.81–43.50

(continued)

Table 2. (continued) Parameters Measured and Primary Results in Studies of Cigarette Smoking and Panic Selected for Review

Study	Parameters Measured	Primary Results
Bernstein et al[31]	Association between age at onset of daily smoking and risk of PD subsequent occurrence	OR = 0.92; 95% CI, 0.86–0.97
Johnson et al[3]	Risk of PD(A) occurrence	
	Subjects smoking > 20 cigarettes/d vs subjects smoking < 20 cigarettes/d	OR = 15.58; 95% CI, 2.31–105.14
	Risk of different anxiety disorders	
	Subjects smoking > 20 cigarettes/d in adolescence and early adulthood vs subjects smoking < 20 cigarettes/d	PD: OR = 7.55; 95% CI, 1.55–36.86 GAD: OR = 3.28; 95% CI, 1.42–7.61
	Risk in early adulthood	
	Subjects smoking > 20 cigarettes/d during adolescence vs subjects smoking < 20 cigarettes/d	PD: OR = 15.58; 95% CI, 2.31–105.14 Agoraphobia: OR = 6.79; 95% CI, 1.53–30.17 GAD: OR = 5.53; 95% CI, 1.84–16.66
Breslau et al[8]	Risk of subsequent onset of different anxiety disorders	
	Pre-existing daily smokers vs nondaily smokers	PD: OR = 2.6; 95% CI, 1.2–5.4 Agoraphobia: OR = 4.4; 95% CI, 2.3–8.0
	Risk of PD	
	Nicotine-dependent current smokers vs nondaily smokers	OR = 2.7; 95% CI, 1.2–6.0
	Elapsed time since quitting and risk of the first onset of psychiatric disorders	PD: OR = 0.5; 95% CI, 0.4–0.7
	Past daily smokers vs nondaily smokers	Agoraphobia: OR = 0.5; 95% CI, 0.5–0.8
Leen-Feldner et al[33]	Factors predicting an increased frequency of panic symptoms	Elevated fear: $\beta = .22$, $sr^2 = 0.02$, $t = 3.90$, $P < .01$ Being a smoker: $\beta = .10$, $sr^2 = 0.008$, $t = 2.19$, $P < .05$
Pohl et al[17]	Prevalence of smoking	
	PD(A) patients at the onset of the illness vs controls	51.6% vs 38.3%, $P = .005$ In women: 53.6% vs 35.1%, $P = .001$
	PD(A) patients at the time of the assessment vs controls	39.7% vs 24.5%, $P = .005$
	Mean age at onset of PD(A)	
	PD(A) patients at the time of the assessment vs controls	In men: PD(A) smokers 29.7 ± 10.1 y vs PD(A) nonsmokers 23.7 ± 12.9 y, $P < .0005$
Amering et al[2]	Mean age at onset of PD(A)	PD(A) smokers had lower age at PD(A) onset than PD(A) nonsmokers, $t = .63$, $P < .05$
Reichborn-Kjennerud et al[34]	Shared factors accounting for the covariance between cigarette smoking and panic	Best-fitting model Environmental factors that affect lifetime daily smoking vs those affecting lifetime panic (rc = 1) Common environmental factors accounted for 75% of the covariance Genetic factors affecting smoking and panic were distinct, ie, specific to each phenotype (ra = 0) Individual specific environmental factors affecting the 2 phenotypes overlap to a small degree (re = 0.25; 95% CI, 0.07–0.44) In the full model Environment factors were perfectly correlated and accounted for 61% of the covariance Genetic factors accounted for 18% of the covariance (ra = 0.17; 95% CI, 0.00–1.00)
Agrawal et al[35]	Correlates of regular smoking	History of PAs: HR = 1.45; 95% CI, 1.11–1.89
Goodwin et al[36]	Risk factors of PAs at the 24th birthday	Parental anxiety and parental smoking: OR = 3.3; 95% CI, 1.0–10.8
Zvolensky et al[37]	Risk factors of PD	Neuroticism and smoking: $\chi^2 = 4.73$, Wald = 4.15, $\beta = .00$, $P < .05$
Brooks et al[38]	Ipaspirone-induced increases in cortisol concentrations PD(A) smokers vs PD(A) nonsmokers	Data not shown, $P < .05$
Zvolensky et al[39]	Anxiety after the challenge and during recovery	
	Smokers with PD vs smokers without PD	B = 15.9, SE = 4.6, $P = .001$
	Smokers with PD vs nonsmokers with PD	B = 13.6, SE = 3.9, $P = .001$
	Bodily distress after the challenge and during recovery	
	Smokers with PD vs smokers without PD	B = 11.3, SE = 4.9, $P = .02$
	Smokers with PD vs nonsmokers with PD	B = 11.0, SE = 4.3, $P = .01$
Cosci et al[42]	Postpatch minus baseline values	Heart rate (beats/min): 6.242 ± 7.168 vs −3.515 ± 11.364, $P = .000$
	Healthy nonsmokers under nicotine vs healthy nonsmokers under placebo	Mean ± SD PSL score: 1.393 ± 2.249 vs −0.030 ± 3.450, $P = .003$
Abrams et al[43]	Over challenge values Smokers vs nonsmokers	Subjective breathlessness: $F_{1, 44} = 69.95$, $P < .02$ Acute Panic Inventory: $t_{45} = 2.11$, $P < .04$

Abbreviations: GAD = generalized anxiety disorder, HR = hazard ratio, NS = not significant, NCS = National Comorbidity Survey, OCD = obsessive-compulsive disorder, OR = odds ratio, PAs = panic attacks, PD = panic disorder, PD(A) = panic disorder with or without agoraphobia, PSL = Panic Symptom List, ra = genetic correlation, rc = shared environmental effects, SP = social phobia, sr^2 = squared semipartial correlation.

Examining clinical samples, Pohl et al[17] showed a rate of smoking in patients with panic disorder with or without agoraphobia at its onset significantly higher than the one observed in healthy controls. They also found a strong gender effect. Indeed, in women, smoking may promote panic disorder onset and persistence; in men, smoking may protect against panic disorder occurrence, since it delays its onset.

These results seem inconsistent with most of the findings presented here. Indeed, Pohl et al[17]suggested that smoking might be a risk factor for the development of panic disorder in women, while the relationship between cigarette smoking and panic disorder might not be a causal one in men. Thus, we argue that gender should be carefully considered in data analyses and interpretation of results.

In Amering et al,[2] smokers with panic disorder with or without agoraphobia were significantly younger at the onset of panic disorder with or without agoraphobia than non- smokers with panic disorder with or without agoraphobia. Thus, age at panic onset should be taken into account in clinical population studies as well as in clinical practice.

Two studies have compared the specificity of smoking in promoting panic disorder among anxiety disorders. Johnson et al[3] found that adolescents who smoked 20 cigarettes or more per day were at elevated risk for generalized anxiety disorder, during both adolescence and early adulthood, and at elevated risk for agoraphobia and generalized anxiety disorder during early adulthood. Breslau et al[8] showed a 4 times greater risk of onset of agoraphobia when associated with pre-existing smoking relative to nonsmoking. These results, consistent with other studies,[27,29] suggest that smoking is linked uniquely to panic among anxiety disorders.

Common Etiology of Shared Vulnerability

Reichborn-Kjennerud et al[34] investigated the hypothesis that a shared vulnerability can account for the relationship between cigarette smoking and panic. They examined shared genetic and environmental liability factors. The results suggest that genetic factors that influence panic and daily smoking appear to be distinct or weakly correlated, while shared environmental factors influencing the 2 phenotypes were highly similar.

Finding consistent results, Agrawal et al[35] examined monozygotic and dizygotic twin pairs and found that a history of panic attacks, together with other environ-mental factors (ie, parental education, parental smoking, early family influences, early life events, and conduct problems), was a significant predictor of regular cigarette smoking.

Goodwin and colleagues[36] focused more on heritabilitythan environmental factors. They showed evidence of an interaction between parental smoking and parental anxiety's influencing the risk of co-occurrence of cigarette smoking and panic attacks among offspring. The authors propose possible explanations: (1) offspring with higher levels of parental anxiety disorders have an inherited (either genetic or environmental) vulnerability to anxiety, thereby they develop anxiety and subsequently begin smoking as a means of self-medication; (2) other behavioral factors associated with anxiety (eg, alcohol consumption) may increase the risk of cigarette smoking initiation; (3) initiation of cigarette smoking among individuals who are vulnerable to anxiety disorders may lead to development of panic attacks through anxiogenic effects or changes in respiratory functioning, and this risk may be more pronounced among those with a familial vulnerability to anxiety disorders;

and (4) the risk of panic related to parental cigarette smoking may be, in part, attributable to changes in respiratory function resulting from exposure to environmental tobacco smoke early in life.

A moderational model studying neuroticism as a possible factor linking smoking and panic disorder was applied to a subsample of the NCS.[37] Current smokers high in neuroticism (ie, a generalized tendency to experience negative affect) smoked greater numbers of cigarettes per day and were the most apt to have a lifetime diagnoses of panic disorder. No such moderating effects were apparent for other anxiety disorders. According to Zvolensky and coworkers,[37] these data suggest that individual differences in theoretically relevant physiologic vulnerability factors (such as neuroticism) may amplify the effects of smoking in terms of panic-related problems.

Mechanisms Underlying the Panic/Smoking Link

The question of whether neurobiologic effects induced by serotoninergic agents are affected by the smoking status of panic disorder with or without agoraphobia patients was examined by Brooks et al.[38] The patients under study underwent a neuropharmacologic challenge with ipaspirone, a selective 5-hydroxytryptamine-1A receptor agonist, and a placebo according to a crossover design. In the group of panic disorder with or without agoraphobia smokers, the ipaspirone-induced increases in cortisol concentrations were about twice as high as in the nonsmoker group. Brooks and coworkers suggested controlling for smoking status in neuroendocrine challenge studies when comparing patients with different psychiatric disorders or patients with healthy controls. According to them, nicotine has to be considered as a psychopharmacological comedication exerting its own effects on certain brain receptors.

Zvolensky et al[39] evaluated anxious and fearful responses to bodily sensations as a function of panic disorder and smoking status. Participants completed a voluntary hyperventilation procedure that elicits panic-relevant bodily sensations. At the postchallenge assessment and recovery period, smokers with panic disorder reported greater levels of anxiety and bodily distress than smokers without panic disorder and nonsmokers with panic disorder. These findings suggested a slower recovery in term of anxiety for smokers with panic disorder than for nonsmokers with panic disorder. Thus, among subjects with panic disorder, a history of regular smoking is related to an increased risk of prolonged anxious responding to bodily sensations.

In recent years, experimental psychiatry has developed different paradigms that allow one to provoke panic in an experimental setting. The CO2 inhalation procedure has proven to be a specific, valid, reliable, and safe way to produce experimental panic.[40] It appears that healthy individuals display a distinct behavioral vulnerability to increasing levels of acute hypercapnia. This effect is dose dependent, and it shares a striking similarity with the psychiatric condition of panic.[41]

Cosci et al[42] tested whether nicotine has a direct influence on laboratory-elicited panic in healthy nonsmoking volunteers. Subjects underwent a 35% CO2 challenge after transdermal administration of a nicotine or placebo patch, according to a crossover design. Compared to the placebo condition, nicotine increased heart rate and panic symptoms prior to the CO2 challenge but did not affect response to

the CO2 challenge itself. The change in physiologic measures before the challenge was attributed to nicotine's impact on autonomic activation.

In a study employing the Read rebreathing method, Abrams and colleagues[43] examined heavy smokers in withdrawal and nonsmokers on subjective and physiologic reactivity to a 4-minute, 5% CO2 challenge. Under the challenge condition, smokers experienced greater subjective breathlessness than did nonsmokers. Despite decreased respiration during the challenge, smokers experienced a significantly greater increase in self-reported cognitive and somatic panic symptoms than nonsmokers. The authors suggested that the findings are consistent with the idea that smoking may promote fearful responses to somatic sensations and, hence, may reflect a panic vulnerability factor.

Although Cosci et al[42] and Abrams et al[43] evaluated subjects without a diagnosis of panic disorder with or without agoraphobia, the 2 studies were not excluded since they are, to our knowledge, the only reports in the literature using a CO2 challenge aimed at clarifying the relationship between smoking and panic.

Experimental studies are strongly heterogeneous in their methods but not in their results. They generally show that regular nicotine use in cigarette smokers or nicotine-dependent individuals leads to exaggerated challenge response, although nicotine use in nicotine-naive individuals does not.[42]

Discussion

Panic and cigarette smoking each appear to have the capacity to serve as a causal factor/facilitator in the development of the other. For example, the bulk of the literature supports a strong relationship between smoking and panic. Few studies are in disagreement. For instance, Black et al[24] found no difference in panic occurrence between smokers and nonsmokers, but when the sample was stratified by gender, they observed such a difference in females. Further studies clarifying the role of gender are warranted.

A large body of literature suggests a specific relationship between smoking and panic relative to other anxiety disorders,* while few authors found such a relationship valid between smoking and other anxiety disorders.[3,7,8,27,28]

However, it is worth noting that 5 of the 11 epidemiologic studies presented here were conducted within the frame- work of the NCS.[26] While the studies referring to the NCS sample strongly support the hypothesis of a specific relationship between smoking and panic, the majority of those referring to non-NCS samples also suggest a link with other anxiety disorders. Thus, the results may have been influenced by the sample under study. Further investigations in samples other than that of the NCS, as well as investigations comparing subjects with different affective diagnoses, are warranted.

The pathogenetic explanations of the co-occurrence between cigarette smoking and panic, highlighted in the studies presented here, refer mainly to 3 hypotheses.

*References 1, 2, 10, 16, 17, 25, 29, 31, 34-39

According to a moderational model, neuroticism is a third factor linking smoking to panic, as it moderates smoking frequency in subjects with a lifetime history of panic.[37]

According to a pathoplastic model of dysfunction, smoking is a vulnerability variable that modifies the expression of panic disorder by exacerbating affective disturbances and negative health processes.[16,33,43] Finally, according to the false suffocation alarm theory, smoking, by increasing the risk of lung disease or impacting the carotid body, may induce an overreaction to suffocation signals and indirectly increase the risk of panic.[10] The first 2 hypotheses have been supported by several studies. However, replication studies mainly derive from the research group of Zvolensky and coworkers[16,33,37] or groups in joint venture with them.[43] Independent groups may lend support to the findings obtained.

With regard to the role of neuroticism, studying the personality of smokers versus nonsmokers who have panic disorder with or without agoraphobia would be fruitful. The idea that smoking may promote fearful responses to somatic sensations could be further developed in order to understand the mechanism by which this process might occur and, hence, help to identify high-risk individuals. For example, it would be interesting to engage comorbid individuals at different levels of nicotine dependence in biologic challenges. Finally, the nature of the respiratory abnormalities in smokers/nonsmokers who have panic disorder with or without agoraphobia and healthy smokers/healthy non- smokers should be compared to better understand the role of smoking in inducing clinical or subclinical abnormalities that may favor panic occurrence.

Some authors found a unidirectional relationship going from smoking to panic [1,2,8,31] Several causal mechanisms may explain this temporal relationship: (1) the biologic models according to which nicotine influences several neurochemical systems, (2) the cognitive perspective of panic attacks, and (3) the cardiovascular effects of nicotine misinterpreted as signs of danger, thus triggering panic attacks according to the Klein model.[14]

On the other hand, only one study showed a bidirectional relationship between smoking and panic.[7]

Some authors found a unidirectional relationship going from smoking to panic [1,2,8,31] Several causal mechanisms may explain this temporal relationship: (1) the biologic models according to which nicotine influences several neurochemical systems, (2) the cognitive perspective of panic attacks, and (3) the cardiovascular effects of nicotine misinterpreted as signs of danger, thus triggering panic attacks according to the Klein model.[14]

On the other hand, only one study showed a bidirectional relationship between smoking and panic.[7]

Experimental studies have been strongly heterogeneous in their methods but not in results. With the exception of Cosci et al,[42] they have consistently found that cigarette smoking increases fear reactivity to a biologic challenge, both in panic disorder patients and healthy volunteers. Cosci et al[42] found that nicotine causes an autonomic activation before a biologic challenge without affecting the response to the challenge itself. However, they studied nonsmokers, rather than smokers and nonsmokers, acutely exposed to nicotine or placebo.[43] Assuming that higher doses of CO2 activate the same physiologic chain of events in panic-free individuals, CO2

challenges may have a strong potential as a substitute for early clinical trials in testing novel pharmacologic compounds.[41]

A few studies evaluated patients with a formal diagnosis of nicotine dependence.[1,7,8,27] Among these studies, consistency was found. Breslau et al[1] and Isensee et al[7] showed that the more severe the level of nicotine dependence, the higher the risk of comorbidity with panic. Farrell et al[27] and Isensee et al[7] found an association not only between nicotine dependence and panic but also between nicotine dependence and generalized anxiety disorder.

It is quite surprising that, although cigarette smoking has been classified among substance use disorders since the 1980s,[23,45] only a minority of studies in the present review referred to this formal diagnosis. Researchers more often defined cigarette smoking according to heterogeneous criteria; less often they assessed nicotine dependence via specific instruments, and only rarely did they use the diagnostic criteria for nicotine dependence. Thus, cigarette smoking seems to be considered a habit of life rather than a disorder. In this framework, it would be desirable to have a larger number of studies assessing nicotine dependence and using the formal diagnosis. This approach would focus on cigarette smoking as a clinically relevant disorder and shed some light on the pathogenetic mechanisms of the co-occurrence between nicotine dependence and panic. Moreover, this approach might have interesting implications for clinical practice and research. In clinical practice, it might encourage health care workers to consider cigarette smoking as a substance use disorder rather than as a habit of life, favor a proper diagnostic assessment, and promote quitting as well as preventive strategies. For research purposes, the use of similar inclusion criteria would very likely improve comparability between studies.

Conclusions

The above evidence suggests that a lifetime association between daily smoking and panic does exist and might reflect causal mechanisms.

Nicotine is a complicated molecule that promotes turnover of several neurotransmitters (eg, acetylcholine, dopamine, norepinephrine) and upregulates the receptors in critical brain areas (eg, the locus ceruleus, mesolimbic dopaminergic pathway).

The following additional studies are warranted: (1) epidemiologic and clinical studies comparing male and female subjects, (2) epidemiologic surveys utilizing new samples, (3) clinical studies comparing the relationship between smoking and panic with the relationship between smoking and other anxiety disorders, (4) experimental studies conducted in independent laboratories, (5) replication of studies focusing on shared vulnerability, and (6) systematic use of the diagnosis of nicotine dependence.

References

1. Breslau N, Kilbey M, Andresti P. Nicotine dependence, major depression, and anxiety in young adults. Arch Gen Psychiatry. 1991;48(12):1069–1074.

2. Amering M, Bankier B, Berger P, et al. Panic disorder and cigarette smoking behaviour. Compr Psychiatry. 1999;40(1):35–38.

3. Johnson JG, Cohen P, Pine DS, et al. Association between cigarette smoking and anxiety disorder during adolescence and early adulthood. JAMA. 2000;284(18):2348–2351.

4. Himle JA, Thyer BA, Fischer DJ. Prevalence of smoking among anxious outpatients. Phobia Practice and Research Journal. 1988;1:25–31.

5. Hayward C, Killen JD, Taylor CB. Panic attacks in young adolescents. Am J Psychiatry. 1989;146(8):1061–1062.

6. De Graaf R, Bijl RV, Smit F, et al. Risk factors for 12-month comorbidity of mood, anxiety, and substance use disorders: findings from The Netherlands mental health survey and incidence study. Am J Psychiatry. 2002;159(4):620–629.

7. Isensee B, Wittchen HU, Stein MB, et al.Smoking increases the risk of panic: findings from a prospective community study. Arch Gen Psychiatry. 2003;60(7):692–700.

8. Breslau N, Novak SP, Kessler RC. Daily smoking and the subsequent onset of psychiatric disorders. Psychol Med. 2004;34(2):323–333.

9. Morissette SB, Brown TA, Kamholz BW, et al. Differences between smokers and nonsmokers with anxiety disorders. J Anxiety Disord. 2006;20(5):597–613.

10. Breslau N, Klein DF. Smoking and panic attacks: an epidemiologic investigation. Arch Gen Psychiatry. 1999;56(12):1141–1147.

11. Pine DS, Klein RG, Coplan JD, et al. Differential carbon dioxide sensitivity in childhood anxiety disorders and nonill comparison group. Arch Gen Psychiatry. 2000;57(10):960–967.

12. Gorman JM, Kent J, Martinez J, et al. Physiological changes during carbon dioxide inhalation in patients with panic disorder, major depression, and

premenstrual dysphoric disorder: evidence for a central fear mechanism. Arch Gen Psychiatry. 2001;58(2):125–131.

13. Caldirola D, Bellodi L, Cammino S, et al. Smoking and respiratory irregularity in panic disorder. Biol Psychiatry. 2004;56(6):393–398.

14. Klein DF. False suffocation alarms, spontaneous panics, and related conditions: an integrative hypothesis. Arch Gen Psychiatry. 1993;50(4): 306–317.

15. Dilsaver SC. Nicotine and panic attacks. Am J Psychiatry. 1987;144(9):1245–1246.

16. Zvolensky MJ, Schmidt NB, McCreary BT. The impact of smoking on panic disorder: an initial investigation of a pathoplastic relationship. J Anxiety Disord. 2003;17(4):447–460.

17. Pohl R, Yeragani VK, Balon R, et al. Smoking in patients with panic disorder. Psychiatry Res. 1992;43:253–262.

18. Jarvik ME, Caskey NH, Rose JE, et al. Anxiolytic effect of smoking associated with four stressors. Addict Behav. 1989;14(4):379–386.

19. Kassel JD, Shiffman S. Attentional mediation of cigarette smoking's effect on anxiety. Health Psychol. 1997;16(4):359–368.

20. Goodwin R, Hamilton SP. Cigarette smoking and panic: the role of neuroticism. Am J Psychiatry. 2002;159(7):1208–1213.

21. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC: American Psychiatric Association; 1987.

22. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.

23. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.

24. Black DW, Zimmerman M, Coryell WH. Cigarette smoking and psychiatric disorder in a community sample. Ann Clin Psychiatry. 1999;11(3):129–136.

25. Lasser K, Boyd JW, Woolhandler S, et al. Smoking and mental illness: A population-based prevalence study. JAMA. 2000;284(20):2606–2610.

26. Kessler RC, Ronald C. National Comorbidity Survey, 1990–1992. Ann Arbor, MI: Inter-University Consortium for Political and Social Research; 2000. [computer file].

27. Farrell M, Howes S, Bebbington P, et al. Nicotine, alcohol and drug dependence and psychiatric comorbidity: results of a national household survey. Br J Psychiatry. 2001;179:432–437.

28. Lopes FL, Nascimento I, Zin WA, et al. Smoking and psychiatric disorders: a comorbidity survey. Braz J Med Biol Res. 2002;35(8):961–967.

29. McCabe RE, Chudzik SM, Antony MM, et al. Smoking behaviors across anxiety disorders. J Anxiety Disord. 2004;18(1):7–18.

30. Goodwin RD, Keyes K, Simuro N. Mental disorders and nicotine dependence among pregnant women in the United States. Obstet Gynecol. 2007;109(4):875–883.

31. Bernstein A, Zvolensky MJ, Schmidt NB, et al. Developmental course(s)of lifetime cigarette use and panic attack comorbidity: an equifinal phenomenon? Behav Modif. 2007;31(1):117–135.

32. Prabhakar NR, Dinerman JL, Agani FH, et al. Carbon monoxide: a role in carotid body chemoreception. Proc Natl Acad Sci U S A.1995;92(6):1994–1997.

33. Leen-Feldner EW, Blanchard L, Babson K, et al. The moderating role of health fear on the relation between smoking status and panic symptoms among adolescents. J Anxiety Disord. 3009;22(5):772–780.

34. Reichborn-Kjennerud T, Roysamb E, Tambs K, et al. Genetic and environmental influences on the association between smoking and panic attacks in females: a population-based twin study. Psychol Med. 2004;34(7):1271–1277.

35. Agrawal A, Madden PA, Heath AC, et al. Correlates of regular cigarette smoking in a population-based sample of Australian twins. Addiction. 2005;100(11):1709–1719.

36. Goodwin RD, Lewinsohn PM, Seeley JR. Cigarette smoking and panic attacks among young adults in the community: the role of parental smoking and anxiety disorders. Biol Psychiatry. 2005;58(9):686–693.

37. Zvolensky MJ, Sachs-Ericsson N, Feldner MT, et al. Neuroticism moderates the effect of maximum smoking level on lifetime panic disorder: a test using an epidemiologically defined national sample of smokers. Psychiatry Res. 2006;141(3):321–332.

38. Broocks A, Bandelow B, Koch K, et al. Smoking modulates neuroendocrine responses to ipsapirone in patients with panic disorder. Neuropsychopharmacology. 2002;27(2):270–278.

39. Zvolensky MJ, Leen-Feldner EW, Feldner MT, et al. Emotional responding to biological challenge as a function of panic disorder and smoking. J Anxiety Disord. 2004;18(1):19–32.

40. Esquivel G, Schruers K, Griez E. Experimental models: panic and fear. In: Blanchard RJ, Blanchard D, Griebel G, et al, eds. Handbook of Anxiety and Fear. Vol. 17. Amsterdam, The Netherlands: Elsevier BV; 2008:413–435.

41. Griez EJ, Colasanti A, van Diest R, et al. Carbon dioxide inhalation induces dose-dependent and age-related negative affectivity. PLoS One. 2007;2(10):e987.

42. Cosci F, Abrams K, Schruers KR, et al. Effect of nicotine on 35% CO2-induced anxiety: a study in healthy volunteers. Nicotine Tob Res. 2006;8(4):511–517.

43. Abrams K, Zvolensky M, Dorflinger L, et al. Fear reactivity to bodily sensations among heavy smokers and non-smokers. Exp Clin Psychopharmacol. 2008;16(8):230–239.

44. World Health Organization. International Statistical Classification of Diseases and Related Health Problems. Geneva, Switzerland: World Health Organization; 1992.

Chapter five

Intensive behavioral therapy for agoraphobia

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Abstract

Background

We investigated the efficacy of an intensive 1-week behavioral therapy program focusing on agoraphobia for panic disorder patients with agoraphobia (PDA).

Design and method

The study design was a case-control study. Main outcome measure was the agoraphobia score of the Fear Questionnaire (FQ-AGO). The outcomes on the FQ-AGO of a 1-week intensive therapy (96 patients) and a twice-weekly therapy (98 patients) were compared.

Results

Agoraphobia improved significantly in both groups, 1 week and 3 months after therapy. Effect size for changes in the 1-week intensive therapy on the FQ-AGO was 0.75.

Limitations

Limitations are use of antidepressants, no placebo group, no long term follow-up.

Conclusion

Behavioral therapy for agoraphobia can be shortened significantly if intensified without affecting therapy outcome, thus allowing patients a more rapid return to work and resumption of daily activities.

Key words: Panic disorder, agoraphobia, behavioral therapy, expanding-spaced exposure, intensive exposure therapy, massed-exposure therapy

Introduction

Panic disorder with agoraphobia (PDA) is an invalidating condition that causes high health care consumption (Barsky et al, 1999; Lepine, 2002; Roy-Byrne et al, 2002; Roy-Byrne et al, 1999; Roy-Byrne et al, 2005; Smit et al, 2009; Zaubler and Katon, 1998). It is associated with higher societal costs compared to other mental disorders regarding direct medical, direct non-medical and indirect non-medical costs (Rees et al, 1998). These costs are even higher if panic disorder is accom-panied by agoraphobia (Batelaan et al, 2007). Several effective therapies are now available for agoraphobia (Sanchez-Meca et al, 2010), mainly cognitive and behavioral therapy (CBT). It is clear that the shorter the duration of the therapy, the sooner the patient can return to his or her normal daily activities, including work.

The present study describes the efficacy of a brief, intensive, clinician-guided exposure program for severe agoraphobia and compares it to a form of behavioral therapy involving twice-weekly contacts with a therapist.

Methods

Subjects

The sample consisted of 194 patients who were recruited from the Academic Anxiety Centre in Maastricht, an outpatient clinic in the Netherlands. Diagnosis according to DSM IV criteria was made by an experienced psychiatrist via psychiatric interview. Only patients with panic disorder with severe agoraphobia as primary diagnosis were included. Exclusion criteria were being on psycho-tropic medication (with the exception of antidepressants), severe depressive disorder, suicidal intent, psychosis, substance abuse or cognitive impairment.

Of the 194 patients, which were included in the study, 96 PDA-patients completed the 1-week in vivo exposure-based behavior therapy program for PDA. This was the experimental group. The matched, historical-control subjects were 98 PDA-patients who completed a twice-weekly therapy program that formerly was the regular treatment at our Academic Anxiety Center.

The study design was a case-control study. The case group consisted of 96 patients. The control group was obtained using data from patients who followed therapy before the introduction of the intensive program. Data from those 98 PDA patients were selected after matching for age, sex, co-morbidity and the use of antidepressants (the antidepressant compound distribution among the 2 treatment groups was as follows, case group and control group respectively: fluvoxamine, 23 and 23; paroxetine, 51 and 51; clorimipramine 1 and 1; sertraline 3 and 1, fluoxetine 3 and 1, moclobemide 1 and 3; citalopram, 4 and 0; trazodone, 1 and 0; desipramine, 0 and 2) . All medication was kept constant, according to the treatment protocol.

Of the 98 patients in the control group, 69 were women and 29 were men. The mean age was 40.01 ± 10.68. Of those 98 patients, 89 patients were taking an antidepressant and 27 patients had a concurrent psychiatric disorder; 13 patients had depressive disorder, 4 patients dysthymic disorder, 1 patient specific phobia and the rest of the 27 patients had combinations of comorbidity (such as depressive disorder, social phobia).

Of the 96 patients in the case group, 73 were women and 23 were men. The mean age was 37.98 ± 9.09. Of those 96 patients, 83 patients were taking an antidepressant and 28 patients had a concurrent psychiatric disorder; 14 patients had depressive disorder, 1 patient obsessive compulsive disorder (OCD), 1 patient specific phobia and the rest of the 28 patients had combinations of comorbidity (such as depressive disorder, social phobia, OCD).

Procedures

The diagnosis of PDA was established in a clinical interview by an experienced psychiatrist following the criteria of the DSM-IV (American Psychiatric Association. and American Psychiatric Association. Task Force on DSM-IV., 2000). Patients also had a medical history inventory and an evaluation through the Mini International Neuropsychiatric Interview (Sheehan et al, 1998) to support the diagnoses.

Psychometric evaluation involved the Fear Questionnaire (FQ) (Marks and Mathews, 1979), the Clinical Anxiety Scale (CAS) (Snaith et al, 1982), and the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). The FQ measures phobic avoidance on three subscales on agoraphobic, social phobic and blood-injury related avoidance (Cox et al, 1995; Marks et al, 1979). Only the total FQ-score (FQ-tot, range 0-120) and the score of the subscale 'agoraphobia' (FQ-AGO, range 0-40) were included in the present study. The researcher who assessed the measures was independent of therapy.

The treatment under investigation was the 1-week in vivo exposure- based behavior therapy program ('the case group') which consisted of 5 full consecutive days of cognitive behavioral therapy. Patients stayed in an inn overnight, while their days were devoted to exposure to several agoraphobic situations. First, the patient received psycho-education on panic disorder and agoraphobia as well as the rationale of exposure therapy. At the beginning, exposure was conducted under full coaching by a behavioral therapist. The coaching was gradually reduced during the week.

The control condition ('the control group') was a twice-weekly therapy program, which consisted of 12 sessions exposure therapy sessions, spread over 6 weeks. The focus of both forms of treatment was on the element of exposure (Sanchez-Meca et al, 2010).

Both therapies included homework and a follow-up program. By practice in their home/daily environment, patients learned to integrate their experiences in other more natural contexts where they used to avoid feared situations. The same therapists trained in behavioral therapy conducted both therapies. All therapies was delivered individually. The amount of face to face time with a therapist did not differ substantially between groups: 23 h in the intensive group versus 23 in the comparison group. Psychometric data were gathered 1 week before and one week after treatment and 3 months after.

Data analysis

Data were analyzed using repeated-measures analysis of variance (ANOVA) with time as the within-subjects factor and type of therapy as the between-subjects factor. The effect size was calculated for FQ-AGO changes in the intensive group. The results were based on a last observation carried forward analysis.

Results

Outcome scores before, 1 week after, and 3 months after therapy are shown in Table 1. Scores of the MADRS and CAS at pre-treatment were significantly higher in the case group. Pre-treatment scores of FQ-tot and FQ-AGO did not differ significantly between groups.

ANOVA of the FQ-AGO scores before, 1 week after, and 3 months after therapy showed a significant improvement in both groups, as can be seen in Figure 1. Effect size for changes in the case group on the FQ-AGO was 0.75. Time*group interactions were not significant for the FQ-AGO.

With regard to the FQ-tot, the MADRS, and the CAS, ANOVA showed a significant improvement in scores on all scales in both groups. Time*group interactions were not significant for the FQ-tot or the MADRS, but they were significant for the CAS, with a stronger improvement in the case group.

Table 1. Outcome scores before, 1 week after, and 3 months after therapy.

	Case group			**Control group**		
	Pre-Treatment	Post-Treatment	3-months after therapy	Pre-Treatment	Post-treatment	3-months after therapy
MADRS	13.0 (6.1)	7.4 (6.0)	7.1 (6.0)	9.2 (7.7)	4.5 (5.7)	4.5 (5.4)
CAS	11.6 (4.4)	5.5 (4.5)	5.4 (4.8)	7.9 (5.5)	3.7 (4.2)	3.6 (4.3)
FQ-tot	52.4 (21.6)	20.4 (14.3)	19.3 (15.9)	57.8 (21.1)	27.2 (21.7)	27.2 (23.0)
FQ-AGO	25.0 (9.8)	5.6 (6.5)	5.5 (10.0)	27.6 (9.0)	9.6 (10.3)	9.9 (10.7)

MADRS: Montgomery–Åsberg Depression Rating Scale; CAS: Clinical Anxiety Scale; FQ-tot: Fear Questionnaire total score; FQ-AGO: Fear Questionnaire 'agoraphobia' subscale score

Limitations

Several limitations of our study need to be mentioned. First, some of the patients were taking an antidepressant. Hence, symptoms were still present in spite of medication. We therefore cannot completely exclude the possibility that medication status may affect treatment outcome. However, an effect of medication is rather unlikely, given that patients were on a constant dosage for 2 months prior to inclusion and medication was kept constant during treatment. Moreover, subjects in the control group were matched on the use of antidepressants. Second, no placebo group was incorporated. Third, since the follow- up data are limited to 3 months, it is not possible to evaluate treatment effect beyond this period. Both therapy programs however, included homework, leading to generalization of fear extinction by extending the treatment out of the therapeutic context, thereby contributing to a more profound treatment effect (Sanchez-Meca et al, 2010). Fourth, patients were not randomly allocated to one of the two treatment programs. However, the data of the control group were selected after matching for age, sex, co-morbidity, and the use of antidepressants.

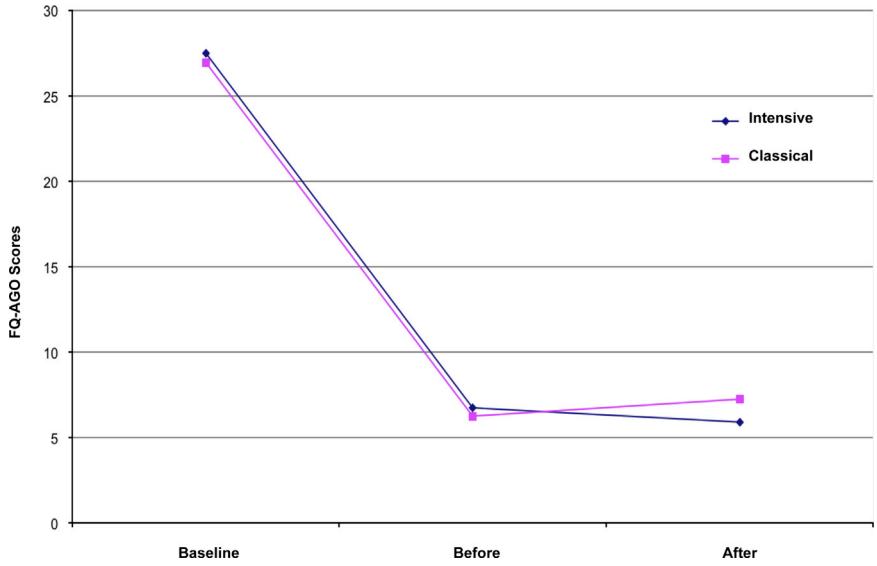

Fig 1. Fear questionnaire-agoraphobia scores (FQ-AGO) before and after treatment with intensive versus classical CBT.

Discussion

This study demonstrated the efficacy of a 1-week intensive behavioral treatment for panic disorder with agoraphobia. Previous studies on the efficacy of intensive therapy versus expanding-spaced exposure have produced mixed results. Lang and Craske (2000) found no differences between a 1-day exposure program and a program with several sessions in 1 week at 1 month of follow-up. However, the interval between the sessions may have been too short to differentiate between the two. Chambless (1990) also found no differences in agoraphobic scores over a 6-month period between ten daily and ten weekly sessions of exposure in 19 agoraphobic patients. On the other hand, Foa et al (1980) compared the efficacy of ten daily sessions of behavior therapy versus ten once-weekly sessions in 11 agoraphobic patients. They found the massed procedure to be superior in reducing agoraphobic avoidance and suggested that this might have been due to the lack of opportunity in this group to engage in avoidance behavior between sessions. Hahlweg et al (2001) studied the effectiveness of 2-3 week daily exposure in 416 PDA patients. Results 6 weeks and 1 year after therapy showed significant reductions in agoraphobic avoidance. No control group was included. Deacon and Abramowitz (2006) found significant reductions in panic disorder symptoms in 10 PD patients, 5 of whom with PDA, after a 2-day cognitive behavioral therapy including cognitive restructuring and exposure in vivo. In a meta-analysis Sanchez-Meca et al (2010) found no relationship between the duration of the therapy and the effect size.

Together with our results, these studies show that behavioral therapy for agoraphobia can be shortened if intensified without affecting therapy outcome. It

has been suggested by Lang et al (2000) that expanding-spaced exposure could be superior in reducing agoraphobia due to exposure to varied contextual stimuli relative to massed exposure. Exposure to varied contextual stimuli may lead to a greater generalization of extinction and less return of fear. The fact that subjects in our case group were exposed to a broad variety of cues may have led to the positive results in the short and longer term.

Conclusions

In conclusion, the 1-week CBT program for agoraphobia allows a more rapid reduction of symptoms with an equally successful therapy outcome. This may result in a more rapid return to work and resumption of daily activities. Another advantage of the time-limited, concentrated design of the 1-week CBT, might be the access to therapy. The availability of an intensive therapy program may not only benefit individual patients, but also have economic returns for society. In attempt to provide cost-effective treatment, the exploration of strategies to shorten the duration of therapy is necessary.

References

American Psychiatric Association., American Psychiatric Association. Task Force on DSM-IV. (2000). Diagnostic and statistical manual of mental disorders : DSM-IV-TR, 4th edn. American Psychiatric Association: Washington, DC, xxxvii, 943 p.pp.

Barsky AJ, Delamater BA, Orav JE (1999). Panic disorder patients and their medical care. Psychosomatics 40(1): 50-56.

Batelaan N, Smit F, de Graaf R, van Balkom A, Vollebergh W, Beekman A (2007). Economic costs of full-blown and subthreshold panic disorder. Journal of affective disorders 104(1-3): 127-136.

Chambless DL (1990). Spacing of exposure sessions in treatment of agoraphobia and simple phobia. Behavior Therapy 21(2): 217-229.

Cox BJ, Endler NS, Swinson RP (1995). An examination of levels of agoraphobic severity in panic disorder. Behaviour research and therapy 33(1): 57-62.

Deacon B, Abramowitz J (2006). A pilot study of two-day cognitive-behavioral therapy for panic disorder. Behaviour research and therapy 44(6): 807-817.

Foa EB, Jameson JS, Turner RM, Payne LL (1980). Massed vs. spaced exposure sessions in the treatment of agoraphobia. Behaviour research and therapy 18(4): 333-338.

Hahlweg K, Fiegenbaum W, Frank M, Schroeder B, von Witzleben I (2001). Short- and long-term effectiveness of an empirically supported treatment for agoraphobia. Journal of consulting and clinical psychology 69(3): 375-382.

Lang AJ, Craske MG (2000). Manipulations of exposure-based therapy to reduce return of fear: a replication. Behaviour research and therapy 38(1): 1-12.

Lepine JP (2002). The epidemiology of anxiety disorders: prevalence and societal costs. The Journal of clinical psychiatry 63 Suppl 14: 4-8.

Marks IM, Mathews AM (1979). Brief standard self-rating for phobic patients. Behaviour research and therapy 17(3): 263-267.

Montgomery SA, Asberg M (1979). A new depression scale designed to be sensitive to change. The British journal of psychiatry : the journal of mental science 134: 382-389.

Rees CS, Richards JC, Smith LM (1998). Medical utilisation and costs in panic disorder: a comparison with social phobia. Journal of anxiety disorders 12(5): 421-435.

Roy-Byrne P, Russo J, Dugdale DC, Lessler D, Cowley D, Katon W (2002). Undertreatment of panic disorder in primary care: role of patient and physician characteristics. The Journal of the American Board of Family Practice / American Board of Family Practice 15(6): 443-450.

Roy-Byrne PP, Stein MB, Russo J, Mercier E, Thomas R, McQuaid J, et al (1999). Panic disorder in the primary care setting: comorbidity, disability, service utilization, and treatment. The Journal of clinical psychiatry 60(7): 492-499; quiz 500.

Roy-Byrne PP, Wagner AW, Schraufnagel TJ (2005). Understanding and treating panic disorder in the primary care setting. The Journal of clinical psychiatry 66 Suppl 4: 16-22.

Sanchez-Meca J, Rosa-Alcazar AI, Marin-Martinez F, Gomez-Conesa A (2010). Psychological treatment of panic disorder with or without agoraphobia: a meta-analysis. Clinical psychology review 30(1): 37-50.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of clinical psychiatry 59 Suppl 20: 22-33;quiz 34-57.

Smit F, Willemse G, Meulenbeek P, Koopmanschap M, van Balkom A, Spinhoven P, et al (2009). Preventing panic disorder: cost-effectiveness analysis alongside a pragmatic randomised trial. Cost effectiveness and resource allocation : C/E 7: 8.

Snaith RP, Baugh SJ, Clayden AD, Husain A, Sipple MA (1982). The Clinical Anxiety Scale: an instrument derived from the Hamilton Anxiety Scale. The British journal of psychiatry : the journal of mental science 141: 518-523.

Zaubler TS, Katon W (1998). Panic disorder in the general medical setting. Journal of psychosomatic research 44(1): 25-42.

Chapter six

The effect of depressive symptoms on behavioral therapy for panic disorder with agoraphobia

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Abstract

Background

The last decades many studies have shown that cognitive behavioral therapy (CBT) is highly effective for the treatment of panic disorder with agoraphobia (PDA). There is a high degree of comorbidity between PDA and depression. However, studies examining treatment outcome for panic disorder with comor-bid depression have produced mixed results.

The goal of this study was to assess the degree of comorbidity between PDA and major depression (MD) in a large outpatient sample and to examine the influence of comorbid MD on treatment outcome for PDA.

Method

Participants were patients referred to an out-patient setting specialized in anxiety disorders. Patients, who met criteria for panic disorder with agoraphobia and completed baseline assessment, were enrolled in the study (N = 689).

For depressive symptoms the Montgomery–Asberg Depression Rating Scale (MADRS) was applied. For PDA symptoms, the Panic and Agoraphobia Scale (PAS) and the subscore for agoraphobia (FQ-AGO) of the Fear Questionnaire were used.

The group that completed the post-treatment assessment was analyzed categorically as well as dimensionally regarding the influence of depression by dividing into 2 groups (comorbid MD or not) or 3 groups (according to their MADRS- score). These groups were then compared regarding their PDA- and depression outcomes at baseline and post-treatment.

Results

Of 689 patients that were enrolled in the study, 421 entered manualized behavioral therapy of which 288 completed the post-treatment assessment. Of these 288 patients, one third had MD (N = 87).

Symptom severity on PDA symptoms at baseline was significantly different between depressed and non-depressed PDA patients. Both depressed and non-depressed PDA patients responded well to behavioral therapy as reflected in post-treatment assessments for depressive and PDA symptoms. Moreover, depressed PDA patients showed even larger improvement than non-depressed PDA patients on the PAS and the MADRS.

Conclusion

Depression frequently accompanies PDA and appears not to affect treatment outcome negatively. Moreover, the depressive symptoms were reduced after manualized behavioral treatment focused on the PDA.

Key words: Panic disorder, agoraphobia, depressive symptoms, major depression, behavioral therapy

Introduction

Clinical studies have demonstrated that different diagnoses may coexist. A large number of epidemiological studies have shown a relationship between anxiety and mood disorders (Angst 1996; Regier et al.,1998).

Psychiatric comorbidity is typically defined as the co-occurrence of two or more psychiatric disorders within the same individual (Maser and Cloninger 1990). Several studies have shown that depression is a frequent comorbid complication of PDA patients (Goodwin et al., 2005; Kessler et al., 1998; Roy-Byrne et al., 2000; Wittchen et al., 1991). There is evidence that anxiety disorders are risk factors for depression and typically precede the onset of depression (Bittner et al., 2004; Goodwin 2002; Wittchen et al., 2003). Moreover, comorbid depression in PDA is associated with more severe panic- related symptoms (Allen et al., 2010; Rief et al., 2000).

Epidemiological studies have shown a one year prevalence rate of PDA of around 3% (Barr Taylor 2006) and a lifetime prevalence rate of 1.5% to 4.7% (Kessler et al., 2006; Mendolowiz and Stein 2000). The lifetime prevalence rate for depressive disorders varies from about 8% (Regier et al., 1990) to 11.7% (Wittchen et al., 1999).

Over a lifetime, about half of patients with panic disorder will develop depression (Barr Taylor 2006). In treatment studies of PD with or without agoraphobia, the comorbidity rate of depression varies between 12% to 47% (Brown et al., 1995; Emmrich et al.,2012; Skeketee et al., 2001; Tsao et al., 2005).

The high comorbidity between PDA and depressive disorder gives rise to ques-tions regarding the influence of a comorbid depression on CBT focusing on the PDA. A clinical implication could be that response to treatment differs between patients with or without comorbid depression.

The last decades, many studies have shown that cognitive behavioral therapy (CBT) is highly effective for the treatment of patients with panic disorder (Beck et al.,1994; Brown and Barlow 1995; Brown et al., 1996; Fava et al., 1995; Sánchez-Meca et al., 2010; Telch et al., 1993). However, studies examining treatment outcome for panic disorder with comorbid depression have produced mixed results. While several studies have suggested that the presence of a concurrent depressive disorder is associated with lesser improvement (Brown and Barlow 1995; Grunhaus et al., 1994; O'Rourke 1996; Rosenberg and Hougaard 2005; Sánchez-Meca et al., 2010; Skeketee et al., 2001; Tsao et al.,1998), other studies suggested that comorbid depression does not negatively affect CBT focusing on PDA (Allen et al., 2010; Dow et al., 2007; Laberge et al., 1993; Maddock and Blacker 1991; Mc Lean et al., 1998; Rief et al., 2000; Tsao et al., 2002).

There are several explanations for these mixed outcomes; the variability in assess-ment procedures, small sample size and associated lack of power to demon-strate possible differences. Also, the tendency in scientific studies to examine homogeneous groups, led in many studies to the exclusion of patients with comorbid depression or to the inclusion of only a low rate of comorbid depression (Blanes and Raven 1995). However, since a comorbid depression in PDA patients is common, the generalizability of the results of some treatment studies can be questioned.

Allen et al. (2010) and Rief et al. (2000) found that, despite having more severe panic disorder symptoms at pretreatment, individuals with comorbid anxiety and/or

depression were equally likely to respond to treatment as those without such depression. However, in the study of Rief et al. (2000) the end-state functioning of PDA patients with comorbid depression was significantly lower than for patients with panic disorder alone.

Recently Emmrich et al. found (2012) that exposure- based cognitive behavioral therapy (CBT) for primary PDA effectively reduces anxiety and depressive symptoms, irrespective of comorbid depression or (severe) depressive symptomatology. These results are in line with previous studies (Tsao 1998, Tsao 2002). On the other hand, in two other studies (Mc Lean et al., 1998; Woody et al., 1999) no significant reduction of depressive symptomatology was found. Those studies however excluded patients with any comorbid axis I disorder other than PD, AG or depression. Also, Allen et al. (2010), found that rates of MDD decreased, but this decrease did not reach statistical significance.

Also, studies examining whether the presence of comorbidity is associated with more severe symptoms of PDA, have yielded conflicting results. Most studies (Allen et al., 2010; Brown et al.1995; Emmrich et al., 2012; Goodwin et al., 2005; Kessler et al., 1998; Rief et al., 2000; Tsao et al., 2002) found that PDA patients with a comorbid diagnosis were rated as having more severe panic symptoms than those without comorbidity. On the other hand, Tsao et al. (1998) found no such difference in their study which may have been due to relatively small sample size.

Clinical studies often aim to include homogeneous subgroups, excluding many types of comorbidity, medication use etc, in search of clear differences between groups. It has been suggested that this approach leads to decreased generalizability of results (Rief et al., 2000). The present study addresses the influence of comorbid depression on treatment effect for panic disorder in a more naturalistic way. We therefore chose not to use very restrictive inclusion criteria. Our goal was to present a sample that is representative for the treatment seeking patients in our outpatient setting.

The current study aims to contribute to the knowledge of the relationship of comorbid MD and PD regarding symptom severity and treatment outcome. The principal aim of the present study was to investigate the effectiveness of manualized behavioral therapy in the treatment of patients with panic disorder and comorbid major depression (MD) compared to PD patients without MD. Hypotheses were formulated as follows: (1) the presence of a comorbid MD is reflected in more severe symptoms of PDA at baseline (2) patients with and without comorbid MD improve to a comparable degree (3) behavioral therapy for PDA also effectively reduces depressive symptomatology as measured with the MADRS.

Methods

Participants were recruited from an outpatient setting specialized in anxiety disorders in Maastricht, the Netherlands.

Patients with the principal diagnosis of PDA according to DSM- IV criteria (APA,1994) were included for baseline assessments (N = 689).

Diagnosis according to DSM IV criteria was made by two experienced psychiatrists via psychiatric interview, including the MINI (Mini International Neuropsychiatric Interview) (Sheehan et al, 1998).

Patients with psychiatric comorbidities were included for manualized behavioral therapy except those conditions expected to severely limit patient participation or adherence (suicidal intent, psychosis, substance abuse or cognitive impairment).

The clinical assessment of fear was performed with two scales: The Fear Questionnaire (FQ) and the Panic and Agoraphobia Scale (PAS). The FQ is a self-rating scale that assesses phobic avoidance. It produces a glo-bal score (FQ-tot, range 0-120) and subscores for agoraphobia (FQ-AGO, range 0-40), blood-injury phobia (FQ-BI, range 0-40) and social phobia (FQ-SOC, range 0-40) (Marks and Mathews, 1979). To assess overall severity of the panic symptomatology, the observer-rated version of the PAS was used (Bandelow et al, 1998). The PAS (range: 0-52) contains 13 items grouped in five subscales: 'Panic Attacks' (including the items frequency, severity and durations), 'Agoraphobia' (including frequency, number and relevance of situations), 'Anticipatory Anxiety' (including frequency and severity), 'Disability' (including family, social relationships and employment) and 'Worries about health' (including worries about health damage by panic attacks and assumption of organic disease). To assess the severity of co-morbid depressive symptoms, the Montgomery-Åsberg Depression Rating Scale (MADRS, range: 0-60) (Montgomery and Asberg, 1979) was used.

The researcher who assessed the psychometric measures was independent of therapy.

After the diagnostic procedure was performed, patients with panic disorder with agoraphobia as principal diagnosis received manualized behavioral therapy (N= 421). The main method was exposure in vivo (Sánchez-Meca et al., 2010). Exposure in vivo is a technique consisting of gradually exposing the patient to feared situations by carrying out experiments.

In those cases where comorbid MD prevented patients from being able to perform exposure exercises, those patients were offered an antidepressant (i.e., SSRI)'.

The duration of the treatment was flexible depending on individual clinical progression, with an average of 12 weeks. Therapy duration and number of sessions did not differ significantly between groups.

Discharge was planned by mutual agreement between patient, behavioral therapist and psychiatrist. At discharge, the initial psychometric assessment was repeated (post-treatment assessment).

Participants.

All patients who fulfilled the criteria of panic disorder with agoraphobia, and completed baseline assessment, were enrolled in the study (N = 689). Of these 421 (61%) entered manualized behavioral therapy and 288 patients (68% of those who entered therapy) completed the post-treatment assessment.

Of the 689 participants, 64% were female, 40% was on an antidepressant, 62.4% had a concurrent psychiatric disorder and 33% had current MD. The mean age was 39 (± 12.5) years, the mean duration of the PDA 11.6 (± 11.2) years, the PAS 23.9 (± 10.3), the FQA 20.3 (± 12.3) and the MADRS 13.8 (± 8.2). Sociodemographic variables of the groups with and without comorbid MD are presented in table 1.

Of the 421 patients who entered manualized behavioral therapy, 66% were female, 40.7% was on an antidepressant and 33% had a comorbid MD. The mean age was

39 (± 12.3) years, the mean duration of the PDA 11.9 (± 11.5) years, the PAS 24.6 (±10.1), the FQA 21.9 (± 11.7) and the MADRS 13.5 (± 7.9).

Of the 288 participants group that completed the post-treatment assessment,

67% were female, 36.5% was on an antidepressant, 62.2% had a concurrent psychiatric disorder and 30.5% had current MD. The mean age was 39.7 (± 12.3) years, the mean duration of the PDA 12.0 (±12.4) years , the PAS 24.1 (± 10.2), the FQA 21.9 (± 11.4) and the MADRS 13.2 (± 7.9).

Data from the last group were analyzed for treatment effect.

Sociodemographic variables of the groups with and without comorbid MD are presented in table 2.

Statistics

To examine the overall effect of treatment on changes in outcome measures, a one-way repeated-measures multiple analysis of variance (MANOVA) was conducted on the FQ-AGO, PAS and MADRS with time (pre-treatment, post-treat-ment) as the within-factor. To examine the impact of depressive symptoms on response to treatment, a one-way independent multiple analysis of covariance (MANCOVA) was used on change scores on the FQ-AGO and PAS (pre minus post scores) with depression severity according to MADRS scores (0-6: symptoms absent, 7-19: mild depression, 19-34: moderate depression and 34-54; severe depression) as the between-factor and duration of illness (Sánchez-Meca et al., 2010) and use of antidepressant during treatment as covariates. For the analysis of baseline values a chi-square test was used for categorical variables (sex, co-morbidity, use of antidepressants) and a one-way ANOVA was used to compare the means of the non-categorical variables (age, duration of the PDA, FQ-AGO pre-treatment, FQ-AGO post-treatment, PAS pre-treatment, PAS post-treatment, MADRS pre-treatment, MADRS post-treatment). The results are presented as means ± standard deviations and significance levels were set at $p < .05$ (two-tailed).

Results

Baseline values

Table 1 shows the sociodemographic variables of the groups with and without comorbid MD at baseline. There were no significant differences considering sex and duration of PDA but there were differences found for age, use of antidepres-sants and co- morbidity (specific phobia, PTSS). There were also striking differences found for the PAS, FQA and MADRS.

Table 2 presents the sociodemographic variables of the participants with and without comorbid MD who completed the post-treatment assessment. There were no significant differences considering sex, age and duration of the PDA but there were differences found for use of antidepressants (at baseline and during therapy) and comorbidity (dysthymic disorder, specific phobia, PTSS). Also here, striking differences were found for the PAS, FQA and MADRS at baseline.

Table 1. Sociodemographics and baseline values

Variable	PDA with MD	PDA without MD	Significance P < 0.05
N	209	421	
Age. years	41.4 ± 12.5	38 ± 12.4	0.001
Females.%	63	64.8	0.371
Duration of the PDA. years	11.6 ± 10.8	11.7 ± 11.5	0.963
Dysthymic disorder	0	23	0.000
Adjustment disorder	0	7	0.102
Bipolar disorder	2	3	0.668
Psychotic disorder	2	4	1.000
Agoraphobia	203	403	0.394
OCD	13	17	0.236
GAD	0	7	0.102
Social phobia	23	27	0.059
Specific phobia	27	89	0.016
Somatoform disorder	17	33	0.877
PTSS	23	12	0.000
Eating disorder	5	4	0.165
Antidepressant. %	47.4	36	0.004
Smoking. %	59.2	41.9	0.000
PAS	29.4 ± 9.3	21.3 ± 9.9	0.000
FQA	24.4 ± 11.4	18.2 ± 12.2	0.000
MADRS	21.8 ± 6.2	9.9 ± 5.9	0.000
SDS	57.2 ± 9.2	43.8 ± 9.8	0.000

There were no significant differences between the 'completers' and the 'non-completers' of the participants entering the manualized behavioral therapy considering age, sex,duration of the PDA, FQA at baseline and MADRS at baseline. There was a difference in antidepressant use ($p = 0.02$) and the PAS at baseline (24.1 ± 10.2 in the 'completers'- group versus 26.9 ± 9.2 in the 'non –completers' group; $p < 0.05$).

Post-treatment values

Table 2 presents the mean FQ-AGO, PAS and MADRS post-treatment scores of the groups with and without MD who completed the post-treatment assessment.

A significant effect of treatment on outcome measures was found [$F(3, 198) = 12.378$, $p < .0001$]. Separate univariate ANOVA's on the PAS and MADRS revealed significant treatment effects [$F(1, 200) = 6.145$, $p < .014$ and $F(1, 200) = 36.718$, $p < .0001$, respectively], but not on the FQ-AGO [$F(1, 200) = .786$, $p = .373$]. Manualized behavioral therapy reduced the intensity of panic symptoms as observed by a significant reduction on the PAS scores. Moreover, behavioral therapy focused on PDA also significantly reduced depressive symptoms. Parameter estimates reveal that compared to individuals without MD patients diagnosed as being depressed have larger PAS change score by 4.263 score-points ($t = 2.249$, $p = .014$). Interestingly, patients with the diagnosis of MD also had a larger MADRS change score by 6.780 score-points when compared to subjects who did not receive the diagnosis ($t = 6.060$, $p < .0001$).

Tabel 2. Sociodemographics values from 'completers'

Variable	PDA with MD	PDA without MD	Significance P < 0.05
N	87	197	
Age. years	40.4 ± 13.1	39.1 ± 12.1	0.418
Females. % (n)	64.4 (n=56)	70 (n=136)	0.438
Duration of the PDA. years	11.4 ± 11.2	12.4 ± 12.4	0.586
Antidepressant. % at baseline	45 (n=40)	32 (n=63)	0.214
Antidepressant. % during therapy	(n=58)	(n=53)	0.000
Smoking. %	53. 8 (n=43)	34.6 (n=66)	0.003
Dysthymic disorder (n)	11	0	0.025
Adjustment disorder	0	3	0.247
Bipolar disorder	1	1	0.551
Psychotic disorder	0	0	
Agoraphobia	87	190	0.075
OCD	6	8	0.309
GAD	0	2	0.346
Social phobia	9	9	0.066
Specific phobia	11	43	0.069
Somatoform disorder	7	20	0.577
PTSS	9	1	0.000
Eating disorder	2	2	0.397
PAS at baseline	29.7 ± 9.8 (n=84)	21.6 ± 9.5 (n=191)	0.000
FQA at baseline	25.9 ± 9.8 (n=87)	20.2 ± 11.7 (n=196)	0.000
MADRS at baseline	21.3 ± 5.9 (n=86)	9.7 ± 5.8 (n=197)	0.000
SDS at baseline	55. 9 ± 9.4 (n=86)	43.4 ± 9.5(=197)	0.000
PAS at posttreatment	7.7 ± 8.3 (n=50)	6.3 ± 6.9 (n=114)	0.269
FQA at posttreatment	8.6± 9.5 (n=55)	6.3 ± 7.5 (n=126)	0.090
MADRS at posttreatment	8.1 ± 6.4 (n=54)	5.1 ± 5.6 (n=121)	0.002
SDS at posttreatment	41.4 ± 11.5 (n=55)	35.7 ± 9.5 (n=126)	0.001

Table 3 presents the mean FQ- AGO and MADRS post- treatment scores of the 3 groups divided according to their MADRS – score on depression severity.

There was a significant effect of treatment on outcome measures [$F(3, 248) = 236.9$, $p < .001$]. Separate univariate ANOVA's on the FQ-AGO, PAS and MADRS also revealed significant treatment effects [$F(1, 250) = 431.8$, $p < .001$, $F(1, 250) = 597.9$, $p < .001$ and $F(1, 250) = 181.9$, $p < .001$, respectively]. Manualized behavioral therapy, as expected, strongly reduced the intensity of symptoms as evidenced by a significant reduction on the FQ-AGO and PAS scores. Interestingly, manualized behavioral therapy specifically focused on PDA (and not on MD) also significantly reduced depressive symptoms.

The impact of depressive symptoms on treatment effect can be seen in figures 1 and 2. There was a significant effect of depressive symptoms on the FQ-AGO and PAS change scores [$F(2, 404) = 2.793$, $p = .026$]. Separate univariate ANOVA's revealed a significant effect of depressive symptoms on PAS change scores [$F(2, 202)=495.9$, $p = .011$] respectively] but not on FQ-AGO change scores [$F(2, 202)=431.8$, $p = .096$]. The duration of illness (years PDA) and the use of an antidepressant during treatment as covariates did not significantly influence the effect of depression on panic measures change scores. Parameter estimates reveal

that compared to individuals with symptoms absent (MADRS: 0-6) patients with mild depression (MADRS: 7-19) have larger PAS change score by 5.269 score-points (t = 2.836, p = .005). Furthermore, patients with a moderate depression (MADRS: 19-34) also had a larger PAS change score by 5.805 score-points when compared to subjects with symptoms absent (t = 2.614, p = .01).

Table 3 Sociodemographics by MD severity

Variable	**MADRS 0-6**	**MADRS 7-19**	**MADRS 20-34**	**Significance P < 0.05**
N=288	N=64	N=160	N=64	
Age years	38.8 (SD 11.1)	39.7 (SD 12.5)	40.2 (SD 12.8)	P<0.804
Females %	36	32.5	32.9	p<0.881
Duration of the PDA. years	9.8 (SD 9.3)	13.3 (SD 13.3)	10.4 (SD 10.8)	P<0.087
Antidepressant % at baseline	28.1 (N = 18)	37.3 (n = 59)	51 (n = 27)	P<0.214
Antidepressant % during therapy	19.4	41.1	57.3	p<0.000
Smoking %	23.3	45	45.5	p< 0.08
Depressive disorder %	0	22.3	82.3	
PAS at baseline	17.0 (SD 9.1)	24.4 (SD 9.2)	30.4 (SD 9.3)	p<0.000
PAS at posttreatment	5.5 (SD 6.0)	8.3 (SD 7.7)	10.6 (SD 9.4)	p<0.004
FQA at baseline	15.6 (SD 11.5)	22.9 (SD 10.7)	25.5 (SD 10.5)	p<0.000
FQA at posttreatment	4.7 (SD 6.6)	7.5 (SD 7.5)	9.5 (SD 9.3)	p<0.002
MADRS at baseline	3.2 (SD 1.9)	12.7 (SD 3.6)	24.6 (SD 3.8)	p<0.000
MADRS at posttreatment	3.3 (SD 3.5)	6.9 (SD 6.2)	11 (SD 8.0)	p<0.000

Discussion

The present study shows that both depressed and non-depressed PDA patients profit from the manualized behavioral treatment focused on the PDA. This result is in line with most recent studies (Allen et al., 2010; Emmrich et al., 2012) on the effects of comorbidity on treatment of PDA.

Although the comorbid group had significantly higher scores on the anxiety scales (PAS, FQA) at baseline, there were no significant differences anymore at post-treatment between both groups. Both groups improved significantly during therapy with a reduction of more than 70% on initial scores on the PAS and a reduction of more than 67 % on initial scores on the FQA.

The improvement of the FQA, as a measure for end- state functioning (Telch et al.,1995) in both groups was also of clinical relevance; in both the depressed and non-depressed group the FQA score was reduced from severe agoraphobia at baseline to agoraphobia in remission at post-treatment. (Cox et al.,1995; Mavissakalian1986)

Figure 1. The impact of depressive symptoms on treatment: FQ-A

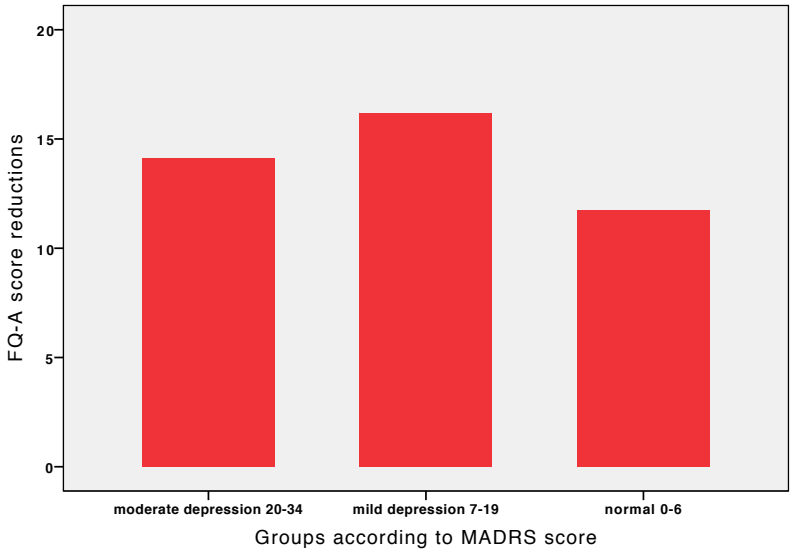
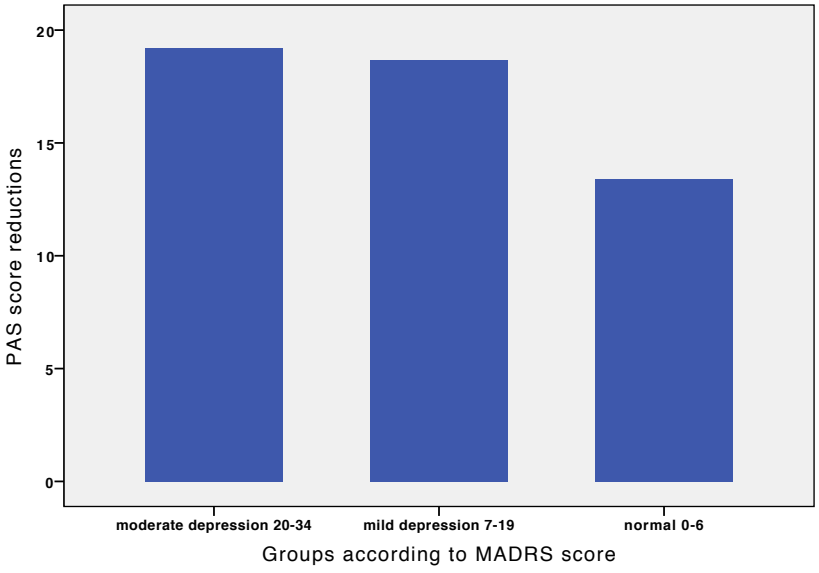


Figure 2. The impact of depressive symptoms on treatment: PAS



The present study also confirmed that manualized behavioral treatment focusing on PDA also effectively reduces depressive symptomatology as measured by the MADRS. This is in line with previous studies (Allen et al., 2010; Rief et al., 2000). Also the recently published study of Emmrich et al., (2012) reports comparable findings. Although the depressed PDA patients still scored significantly higher at post-treatment on the MADRS than did the non-depressed PDA patients, there was a significant effect of treatment on the depressive symptoms in both groups.

The improvement of the MADRS in both groups was also of clinical relevance; in the depressed group the MADRS score was reduced from "moderate" depress-sion at baseline to "mild" at post-treatment and in the non-depressed group from "mild depression" at baseline to no depressive symptoms at post-treatment (Montgomery and Asberg, 1979).

Our hypothesis that PDA patients with comorbid MD tend to show more severe symptomatology than non-depressed PDA patients at baseline, could be con-firmed for the specific PDA rating scales (PAS and FQA). These results are per-fectly in line with recent studies (Allen et al., 2010; Emmrich et al., 2012). Moreover, even the severity of the panic disorder, measured with the PAS, in our study (depressed and non- depressed group) is comparable with the findings of Emmrich. Unfortunately, since Emmrich et al. (2012) used another instrument for agoraphobia, no comparison can be made regarding severity of agoraphobic avoidance.

As could be expected, also the specific depression assessment MADRS showed significantly higher scores for the depressed group.

We defined comorbidity as the simultaneous coexistence of 2 disorders accor-ding to full DSM – IV criteria. Investigating the prevalence of depressive disorder as a comorbid diagnosis, we found a point prevalence of depressive disorder of 33 % in our sample of PDA patients at baseline, in the sample that entered manualized behavioral therapy and also in those who completed treatment. This percentage was well within the range we expected on the basis of earlier clinical studies (Brown et al., 1995; Emmrich et al., 2012; Steketee et al., 2001; Tsao et al., 2005). At baseline, and also in the group of the 'completers', we found a concurrent psychiatric disorder in 62 % of the patients, which is also in line with previous studies (Brown and Barlow 1992; Brown et al., 1995). No difference was found between the group at baseline, the group that entered the manualized behavioral therapy and the group that completed the manualized behavioral therapy regarding sex, age, duration of PDA, comorbidity and baseline assess-ment (PAS, FQA, MADRS). There were also no significant differences between the 'completers' and the 'non- completers' of the patients entering the manualized behavioral therapy considering age, sex, duration of the PDA, FQA and MADRS at baseline.

The fact that the sociodemographic and clinical characteristics at baseline were similar in the different 'consecutive' samples (e.g. at baseline, entering behavioral therapy and completing therapy) is of major importance as our sample was treated in a setting of routine clinical care. Thus, it was not specifically the most depressed or severely ill patients who were lost to follow- up.

Some shortcomings of this study must be mentioned. First, as a result of liberal inclusion criteria, additional comorbidity next to MD, were present in our samples. Second, the mean MADRS score at baseline of the depressed group that entered manualized behavioral therapy for PDA appeared to reflect depressive disorder of

only moderate severity. However, previous studies showed similar findings (Emmrich et al., 2012). A possible explanation for this finding can be the organization of mental health care in the Netherlands, where severely depressed patients are first referred to specialized mood disorder clinics for treatment of the depression. Therefore, we cannot exclude the possibility that PDA patients with a severe depression were preferentially referred to a mood-disorders clinic.

Third, the nature of the study design precludes follow- up analysis to explore the relationship of manualized behavioral therapy for panic disorder to comorbidity over time. Nevertheless, several studies found that positive treatment effects are retained or even enhanced in the follow- up period (Emmrich et al., 2012; Tsao et al.1998; Tsao et al., 2002; Tsao et al., 2005).

Finally, some of the patients were taking an antidepressant. Hence, symptoms were still present in spite of medication. However, the analyses did not show a significant influence of medication use on the patterns of change of the assessments (PAS, FQA, MADRS).

At the same time, one should define some of the above weak points in relation to the positive points of this study, among which is its naturalistic nature. Our sample is directly taken from day-to-day clinical practice, which is relevant for patients in the clinical setting. As such, the characteristics of patients in this study can be regarded as typical for help seeking patients with PDA in an outpatient setting.

Furthermore, the strengths of this study include (a) a large sample size generated from a single center, (b) substantial statistical power to examine our hypotheses, (c) the use of both clinician - rated and self- report measures on panic and depressive symptoms, (d) carefully use of state of the art manualized behavioral therapy for PDA (e) diagnostic assessments conducted by independent evaluators, (f) categorical and dimensional examination of the effect of depression and depressive symptomatology on the therapy focusing on PDA.

The current study examined in a large group of outpatients if comorbid MD has a negative influence on treatment outcome for manualized behavioral therapy for PDA. We found that although the depressed PDA group was associated with more severe panic disorder symptoms at baseline, the treatment response was comparable in the depressed versus the non-depressed PDA group. Also, the manualized behavioral therapy for PDA reduced the severity of co-occurring depressive symptoms in both groups.

These data suggest that comorbid MD is not an obstruction to treatment response and successful treatment of panic disorder is associated with reductions of comorbid depressive symptoms. These data support the notion that it is possible to treat both MD and PDA at the same time without having to adapt the therapeutic strategy for addressing the associated depressive symptomatology.

References

Allen Laura B. , Kamila S. White, David H. Barlow, M. Katherine Shear, Jack M. Gorman, and Scott W. Woods. Cognitive-Behavior Therapy (CBT) for Panic Disorder: Relationship of Anxiety and Depression Comorbidity with Treatment Outcome J Psychopathol Behav Assess. Jun 2010; 32(2): 185–192

American Psychiatric Association (APA).1994. Diagnostic and Statistical Manual of Mental Disorder. Washington, DC.

Andrade L, Eaton WW, Chilcoat HD. Lifetime co-morbidity of panic attacks and major depression in a population-based study: age of onset. Psychol Med. 1996 Sep;26(5):991-6.

Angst J: Comorbidity of moods disorders: a longitudinal prospective study. Br J Psychiatry 1996;168(suppl.30),31-37

Bandelow, B., Brunner, E., Broocks, A., Beinroth, D., Hajak, G., Pralle, L., Ruther, E., 1998. The use of the Panic and Agoraphobia Scale in a clinical trial. Psychiatry research 77, 43-49.

Barr Taylor C. Clinical Review. Panic disorder BMJ Volume 332

Barlow DH, Lehman CL. Advances in the psychosocial treatment of anxiety disorders. Implications for national health care. Arch Gen Psychiatry. 1996 Aug;53(8):727-35.

Beck JG, Stanley MA, Baldwin LE, Deagle EA 3rd, Averill PM. Comparison of cognitive therapy and relaxation training for panic disorder. J Consult Clin Psychol. 1994 Aug;62(4):818-26.

Bittner A, Goodwin RD, Wittchen HU, Beesdo K, Höfler M, Lieb R. What characteristics of primary anxiety disorders predict subsequent major depressive disorder? J Clin Psychiatry. 2004 May;65(5):618-26, quiz 730.

Blanes T, Raven P: Psychotherapy of panic disorder. Curr Opin Psychiatry 1995;8:167-171

Brown TA, Barlow DH. Comorbidity among anxiety disorders: implications for treatment and DSM-IV. J Consult Clin Psychol. 1992 Dec;60(6):835-44.

Brown TA, Antony MM, Barlow DH. Diagnostic comorbidity in panic disorder: effect on treatment outcome and course of comorbid diagnoses following treatment. J Consult Clin Psychol. 1995 Jun;63(3):408-18

Brown TA, Barlow DH. Long-term outcome in cognitive-behavioral treatment of panic disorder: clinical predictors and alternative strategies for assessment. J Consult Clin Psychol. 1995 Oct;63(5):754-65.

Brown C, Schulberg HC, Madonia MJ, Shear MK, Houck PR. Treatment outcomes for primary care patients with major depression and lifetime anxiety disorders. Am J Psychiatry. 1996 Oct;153(10):1293-300.

Brown TA, Campbell LA, Lehman CL, Grisham JR, Mancill RB. Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. J Abnorm Psychol. 2001 Nov;110(4):585-99.

Cox BJ, Endler NS, Swinson RP (1995). An examination of levels of agoraphobic severity in panic disorder. Behaviour research and therapy 33(1): 57-62.

Dow MG, Kenardy JA, Johnston DW, Newman MG, Taylor CB, Thomson A.

Prognostic indices with brief and standard CBT for panic disorder: I. Predictors of outcome. Psychol Med. 2007 Oct;37(10):1493-502.

Emmrich A, Beesdo-Baum K, Gloster AT, Knappe S, Höfler M, Arolt V, Deckert J, Gerlach AL, Hamm A, Kircher T, Lang T, Richter J, Ströhle A, Zwanzger P, Wittchen HU. Depression does not affect the treatment outcome of CBT for panic and agoraphobia: results from a multicenter randomized trial. Psychother Psychosom. 2012;81(3):161-72.

Fava GA, Zielezny M, Savron G, Grandi S. Long-term effects of behavioural treatment for panic disorder with agoraphobia. Br J Psychiatry. 1995 Jan;166(1):87-92.

Goodwin RD, Faravelli C, Rosi S, Cosci F, Truglia E, de Graaf R, Wittchen HU. The epidemiology of panic disorder and agoraphobia in Europe. Eur Neuropsychopharmacol. 2005 Aug;15(4):435-43.

Goodwin RD. Anxiety disorders and the onset of depression among adults in the community. Psychol Med. 2002 Aug;32(6):1121-4.

Grunhaus L, Pande AC, Brown MB, Greden JF. Clinical characteristics of patients with concurrent major depressive disorder and panic disorder. Am J Psychiatry. 1994 Apr;151(4):541-6.

Kessler RC, Stang PE, Wittchen HU, Ustun TB, Roy-Burne PP, Walters EE. Lifetime panic-depression comorbidity in the National Comorbidity Survey. Arch Gen Psychiatry. 1998 Sep;55(9):801-8.

Kessler RC, Chiu WT, Jin R, Ruscio AM, Shear K, Walters EE. The epidemiology of panic attacks, panic disorder and agoraphobia in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2006 Apr;63(4):415-24.

Laberge B, Gauthier JG, Côté G, Plamondon J, Cormier HJ. Cognitive-behavioral therapy of panic disorder with secondary major depression: a preliminary investigation. J Consult Clin Psychol. 1993 Dec;61(6):1028-37.

Maddock RJ, Blacker KH. Response to treatment in panic disorder with associated depression. Psychopathology. 1991;24(1):1-6.

Marks IM, Mathews AM. Brief standard self-rating for phobic patients. Behav Res Ther. 1979;17(3):263-7.

Maser, J.D., & Cloninger, C.R. (eds). (1990). Comorbidity of mood and anxiety disorders. Washington, DC: American Psychiatric.

Mavissakalian, M., 1986. Clinically significant improvement in agoraphobia research. Behaviour research and therapy 24, 369-370

McLean PD, Woody S, Taylor S, Koch WJ. Comorbid panic disorder and major depression: implications for cognitive-behavioral therapy. J Consult Clin Psychol. 1998 Apr;66(2):240-7.

Mendlowicz, M.D. and Murray B.Stein, M.D. Quality of life in Individuals With Anxiety Disorders. Am J Psychiatry 2000; 157:669-682.

Montgomery SA, Asberg M (1979). A new depression scale designed to be sensitive to change. The British journal of psychiatry : the journal of mental science 134: 382-389.

O'Rourke D, Fahy TJ, Brophy J, Prescott P. The Galway Study of Panic Disorder. III. Outcome at 5 to 6 years. Br J Psychiatry. 1996 Apr;168(4):462-9.

Regier DA, Rae DS, Narrow WE, Kaelber CT, Schatzberg AF. Prevalence of anxiety disorders and their comorbidity with mood and addictive disorders. Br J Psychiatry Suppl. 1998;(34):24-8.

Regier DA, Narrow WE, Rae DS. The epidemiology of anxiety disorders: the Epidemiologic Catchment Area (ECA) experience. J Psychiatr Res. 1990;24 Suppl 2:3-14.

Rief W, Trenkamp S, Auer C, Fichter MM. Cognitive behavior therapy in panic disorder and comorbid major depression. A naturalistic study. Psychother Psychosom. 2000 Mar-Apr;69(2):70-8.

Rosenberg NK, Hougaard E. Cognitive-behavioural group treatment of panic disorder and agoraphobia in a psychiatric setting: A naturalistic study of effectiveness. Nord J Psychiatry. 2005;59(3):198-204.

Roy-Byrne PP, Stang P, Wittchen HU, Ustun B, Walters EE, Kessler RC. Lifetime panic-depression comorbidity in the National Comorbidity Survey. Association with symptoms, impairment, course and help-seeking. Br J Psychiatry. 2000 Mar;176:229-35.

Sánchez-Meca J, Rosa-Alcázar AI, Marín-Martínez F, Gómez-Conesa A. (2010). Psychological treatment of panic disorder with or without agoraphobia: a meta-analysis. Clinical psychology review 30(1): 37-50.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of clinical psychiatry 59 Suppl 20: 22-33;quiz 34-57.

Steketee G, Chambless DL, Tran GQ. Effects of axis I and II comorbidity on behavior therapy outcome for obsessive-compulsive disorder and agoraphobia. Compr Psychiatry. 2001 Jan-Feb;42(1):76-86.

Telch MJ, Lucas JA, Schmidt NB, Hanna HH, LaNae Jaimez T, Lucas RA. Group cognitive-behavioral treatment of panic disorder. Behav Res Ther. 1993 Mar;31(3):279-87.

Telch MJ, Schmidt NB, Jaimez TL, Jacquin KM, Harrington PJ: Impact of cognitive-behavioral treatment on quality of life in panic disorder patients. J Consult Clin Psychol 1995; 63:823–830

Tsao JC, Lewin MR, Craske MG.The effects of cognitive-behavior therapy for panic disorder on comorbid conditions. J Anxiety Disord. 1998 Jul-Aug;12(4):357-71.

Tsao 2002: Effects of Cognitive.;Replication and extension. Behavior Therapy 2002; 33:493-509

Tsao JC, Mystkowski JL, Zucker BG, Craske MG. Impact of cognitive-behavioral therapy for panic disorder on comorbidity: a controlled investigation. Behav Res Ther. 2005 Jul;43(7):959-70.

Wittchen HU, Essau CA, Krieg JC: Anxiety disorders- similarities and differencies of comorbidity in treated and untreated groups. Br J Psychiatry 1991;159:23-33

Wittchen HU, Beesdo K, Bittner A, Goodwin RD. Depressive episodes-evidence for a causal role of primary anxiety disorders? Eur Psychiatry. 2003 Dec;18(8):384-93.

Wittchen HU, Lieb R, Wunderlich U, Schuster P. Comorbidity in primary care: presentation and consequences. J Clin Psychiatry. 1999;60 Suppl 7:29-36; discussion 37-8.

Woody S, McLean PD, Taylor S, Koch WJ. Treatment of major depression in the context of panic disorder. J Affect Disord. 1999 May;53(2):163-74.

Chapter seven

Therapygenetics: 5-HTTLPR genotype predicts the response to exposure therapy for agoraphobia

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Abstract

This study was intended to assess the extent to which the low- expression allele of the serotonin transporter gene promoter predicts better response to exposure-based behavior therapy in patients with panic disorder with agoraphobia (PDA). Ninety-nine patients with PDA underwent a 1-week in vivo exposure-based behavior therapy program and provided saliva samples to extract genomic DNA and classify individuals according to four allelic forms (SA, SG, LA, LG) of the 5-HTT-linked polymorphic region (5-HTTLPR). We determined whether the 5-HTTLPR genotype predicted change in avoidance behavior in PDA following treatment. After controlling for pre-treatment avoidance behavior, the 5-HTTLPR low-expression genotypes showed a more favorable response to exposure therapy two weeks following treatment, compared to the other patients. This study suggests a genetic contribution to treatment outcome following behavior therapy and implicates the serotonergic system in response to exposure-based treatments in PDA.

Key words: Behavior therapy, exposure therapy, genetics, panic disorder, agoraphobia, serotonin.

Introduction

The serotonin transporter length polymorphism (5-HTTLPR) has received much attention over the last years in the study of gene-environment (GxE) interactions in emotional disorders. Many studies, including meta-analyses, reported an interaction with a variety of environmental factors while others failed to find such a relationship (Colasanti et al., 2011; Feinn et al., 2005; Karg et al., 2011; Minelli et al., 2011; Pergamin-Hight et al., 2012; Schinka, 2005; Schinka et al., 2004; Serretti et al., 2006).

An explanation for this apparent contradiction has been proposed, in that an interaction effect between the 5-HTTLPR and the environment is not of a general nature but is restricted to some specific environmental factors (Blaya et al., 2007; Minelli et al., 2011; Munafo et al., 2008).

Stein et al. (2008) found in young adults a statistically significant interaction between 5-HTTLPR genotype and levels of childhood (emotional or physical) maltreatment. Specifically, SS individuals with higher levels of maltreatment had significantly higher levels of anxiety sensitivity. Klauke et al. (2011) showed a GxE effect of more active 5-HTT genotypes and childhood maltreatment on anxiety sensitivity. These two studies provide evidence of a genetic influence on anxiety sensitivity and this effect is modified by severity of childhood maltreatment. Further, it has also been demonstrated that 5-HTTLPR SS-homozygotes who experienced 2 or more separation life events showed a significantly higher prevalence of panic disorder compared to those with SL- heterozygotes or LL-homozygotes. Also, 5-HTTLPR SS-homo- zygotes who experienced more separation life events showed a significantly higher harm avoidance (Choe et al., 2013). Together, these findings are consistent with the notion that 5- HTTLPR operates broadly to moderate emotional response to stress. The issues of replication and specificity also apply to the study of the effect of 5-HTTLPR genotype on the therapy response in psychiatric disorders.

Considerable effort is invested in elucidating the genetic factors that determine and can predict the effects of pharmacological therapy for psychiatric disorders (Arias et al., 2003; Keers and Aitchison, 2011; Kim et al., 2006; Perna et al., 2005; Serretti et al., 2006; Taylor et al., 2010; Zanardi et al., 2001). Equally important but much less studied is the influence of genetic variation on the efficacy of psychological therapy. It is both of theoretical and clinical interest to identify biological markers for individualization of cognitive behavior therapy (CBT) associated with successful outcome. These studies may give us a more nuanced understanding of psychopathology, which in turn can enhance the ability to tailor treatments individually based on genetic profile, thereby increasing the effectiveness of psychological treatments. This way, 'therapygenetics', similar to pharmacogenetics (Keers and Aitchison, 2011), may have the potential to determine who is more likely to respond to which form of treatment (e.g. CBT, drugs or both).

Currently, there is a lack of studies investigating the role of genetic variants in the efficacy of CBT in panic disorder with agoraphobia (PDA). Traditionally, CGT was considered to exert its effect via psychosocial mechanisms in contrast with pharmacological treatment, which was considered to act via biological mechanisms. However, research has clearly shown that the changes in affect, behavior and cognition seen after CBT have biological underpinnings and are accompanied by significant and disorder specific changes in brain metabolism (Goossens et al., 2007; Linden, 2006; Roffman et al., 2005).

The genetic contribution to the liability of PDA is around 30–40% (Hettema 2001). In the case of anxiety disorders, several studies have suggested a genetic contribution to treatment outcome following CBT (Bryant et al., 2010; Eley et al., 2012; Hudson et al., 2013; Kim et al., 2006; Lester et al., 2012; Lonsdorf et al., 2010; Reif et al., 2014). The study of Bryant et al. (2010), in patients with posttraumatic stress disorder (PTSD), showed that six months after treatment, the 5-HTTLPR low-expression genotype group (S or LG allele carriers) still displayed more severe PTSD-symptoms relative to the other patients. Eley et al. (2012) found that the type of 5-HTTLPR predicted response to CBT among children with anxiety disorders. Specially, children with two copies of the low-expressing S-allele had better symptomatic response to treatment at follow-up (i.e., 6 months after completion of CBT) than children with one or two copies of the L-allele. Lonsdorf et al. (2010) demonstrated that panic disorder patients with the COMT- val158met/met genotype might profit less from (exposure-based) CBT treatment methods as compared to patients carrying at least one val-allele. In this study, no association was found with the 5-HTTLPR/rs25531 genotypes. Kim et al. (2006) showed that the BDNF Val66Met genotype predicts response to cognitive behavior therapy in PTSD. Focusing on neurotrophic genes, Lester et al. (2012) demonstrated in a sample of 374 anxiety-disordered children, that children with one or more copies of the T allele of nerve growth factor (NGF rs6330) were significantly more likely to be free of their primary anxiety diagnosis at follow-up. No signifi- cant associations were observed between brain-derived neutrotrophic factor (BDNF rs6265) and response to psycho- logical therapy. The same group followed up on these

findings, this time using a 'risk index' approach combining demographic and clinical data with genetic data (5HTTLPR and NGF rs6330) to predict outcome of CBT in a group of anxious children. Results showed that children scoring high on this index were considerably more likely to retain their primary anxiety disorder at follow-up (Hudson et al., 2013). In a very recent paper, Reif et al. (2014) report on the impact of MAOA-uVNTR on therapy response, behavioral avoidance and brain activity during fear conditioning in a study on CBT in PDA. The results showed that patients with the long MAOA risk alleles (causing higher activity of MAO- A) profit less from exposure- based CBT as reflected by lower response rates. During exposure to a standarized behavior avoidance test, high- risk patients also reported higher anxiety, more panic attacks and elevated heart rate. Furthermore, fMRI scanning during a classical fear-conditioning paradigm in a subset of these patients (n = 42) demonstrated that patients carrying the protective allele showed increased activation of the anterior cingulate cortex (ACC) upon presentation of the CS+ during acquisition of fear. Such activation was absent in high-risk allele carriers

In line with our previous work on the role of the serotonin system in PDA (Colasanti et al., 2011; Kim et al., 2006; Schruers and Griez, 2003, 2004; Schruers et al., 2000; Schruers et al.,

2002) and more specifically of the 5-HTTLPR (Schruers et al., 2011), we focused on the role of the 5-HTTLPR.

In the present study, we investigated the effect of variation in the 5-HTTLPR gene on the efficacy of a one- week intensive exposure-based therapy for agoraphobia in a sample of patients with PDA. In line with the study of Eley et al. (2012), we hypothesized that the S-allele would be associated with enhanced response to therapy.

Materials and methods

Participants

Ninety-nine patients of white European heritage who completed the 1-week in vivo exposure-based behavior therapy program for PDA at the Academic Anxiety Centre in Maastricht, an outpatient clinic in the Netherlands, participated in the study. Only patients with PD with agoraphobia as primary diagnosis were included. Exclusion criteria were being on psychotropic medication (with the exception of antidepressants), severe depressive disorder, suicidal intent, psychosis, substance abuse or cognitive impairment. Of the ninety-nine patients, 33 patients were taking an antidepressant and 55 patients had a concurrent psychiatric disorder; 30 patients had depressive disorder, 5 patients dysthymic disorder, 1 patient adjustment disorder, 1 patient bipolar disorder, 5 patients social phobia, 20 patients specific phobia, 3 patients OCD, 4 patients PTSD, 2 patients GAD, 8 patients somatoform disorder and 2 patients an eating disorder. The study was approved by the local medical ethics committee and all patients gave their informed consent after a detailed explanation of the procedure.

Procedure

Participants were recruited from our outpatient setting. Diagnosis according to DSM IV criteria was made by two experienced psychiatrists via psychiatric interview, including the MINI (Mini International Neuropsychiatric Interview) (Sheehan et al., 1998).

Further clinical assessment of anxiety was performed with two scales: The Fear Questionnaire (FQ) is a self- rating scale that assesses phobic avoidance. It produces a global score (FQ-tot) and subscores for agoraphobia (FQ- AGO), blood-injury phobia (FQ-BI) and social phobia (FQ- SOC) (Marks and Mathews, 1979). Since the therapy mainly focused on avoidance behavior, the FQ-AGO was chosen as main outcome variable. To assess overall severity of the panic symptomatology, the Panic and Agoraphobia Scale (PAS) was used (Bandelow et al., 1998). De PAS contains 13 items grouped in five subscales: 'Panic Attacks' (including the items frequency, severity and durations), 'Agoraphobia' (including frequency, number and relevance of situations),

'Anticipatory Anxiety' (including frequency and severity),

'Disability' (including family, social relationships and employment) and 'Worries about health' (including worries about health damage by panic attacks and assumption of organic disease). The observer-rated version of the PAS was used. Psychometric evaluation involved also the Montgom- ery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) to assess the severity of co-morbid depressive symptoms.

The 1-week intensive, exposure-based behavioral therapy program for agoraphobia consisted of 5 full consecutive days of therapy. The patients' days were devoted to exposure to several agoraphobic situations. At first, exposure was con- ducted under full coaching by a licensed behavioral thera- pist. Coaching was gradually reduced during the week. Psychometric data were gathered before (approximately 6 weeks) and 2 weeks after treatment. The researcher who assessed the measures was independent of therapy. In the period between the first

psychometric assessment and the start of therapy, general information was provided (group- wise, together with patients with other anxiety disorders) on the procedures at the Academic Anxiety Center. In the week immediately before the start of the actual exposure treatment, each patient individually received detailed information on the treatment, however still without any therapy exercises or assignments.

Genetic analysis

Saliva samples for DNA isolation were collected in Oragene DNA Collection kits (DNAgenotek, Ottawa, Canada). Genomic DNA was extracted using the AutoGenFlex DNA isolation system (Autgen, Hilliston, MA, USA) according manufacturer's instructions.

On the 5-HTTLPR locus, rs25531 is a functional variant that defines a tri-allelic genotype, which consists of the LA, LG and SA alleles (SG is rare). The LG and S alleles have similar expression levels. Phase-known HTTLPR and rs25531 were determined by a modification of the procedure by Wendland (2006).

Fragment sizes and corresponding genotypes were independently scored by two technicians. Genotype frequencies in the total sample (n = 99) were as follows: LALA, 34; LALG, 7 ;LGLG, 0 ;SALA, 35 ;SALG, 4; SGLG, 0; SASA, 19; and SASG, 0.

In the analysis, the tri- allelic 5-HTTLPR genotype was expressed according to the level of expression as follows: LGS, LGLG and SS as SS; LAS and LALG as LS; and LALA as LL. The distribution of genotypes (LL: 34,3 %, LS: 41,4 %, SS: 24,2 %) was in Hardy-Weinberg equilibrium. At posttreatment data of all 99 patients were available. The bi-/tri-allelic 5-HTTLPR locus was the only genetic marker tested in this study.

Statistical analyses

To examine the impact of 5-HTTLPR genotype on response to exposure treatment, a two-way analysis of variance (ANOVA) with repeated measures was conducted on the FQ-AGO and PAS with 5-HTTLPR group (SS, SL and LL) as the between factor and time (pre-treatment, post-treatment) as the within-factor. Chi-square test was used for categorical variables (sex, co-morbidity, use of antidepressants). To compare the means of the non-categorical variables, a one-way ANOVA was used (age, duration of the PDA, FQ-AGO pre-treatment, FQ-AGO post-treatment, PAS pre-treatment, PAS post-treatment, MADRS pre-treatment, MADRS post-treatment). The results are presented as means ± standard deviations and significance levels were set at $p<0.05$ (two-tailed).

Results

Demographic and clinical Data

There were no significant differences between the three groups in terms of sex, age, duration of the PDA. There were also no significant differences in antidepressant use and/nor comorbidity (table 1).

Treatment response

Table 2 presents the mean avoidance behavior severity (FQ-AGO) pre-treatment and post-treatment, and the impact of5-HTTLPR genotype on treatment response can be seen in fig. 1.

There was a significant effect of treatment as measured by the FQ-AGO and PAS [$F(1, 96)=347.6$, $p<0.001$ and $F(1, 84)=239.3$, $p<0.001$, respectively]. Intensive exposure-based behavior therapy, as expected, strongly reduced the intensity of symptoms as evidenced by a significant reduction on the FQ-AGO and PAS scores.

There was also a significant treatment X genotype interaction effect as measured by the FQ-AGO and PAS [$F(2, 96)=4.0$, $p=0.02$ and $F(2, 84)=3.3$, $p=0.041$; respectively]. Post hoc comparison shows that after therapy patients with the LL genotype have a smaller FQ-AGO score reduction when compared with patients with the SS genotype and the SL genotype [$t(56)=-2.724$, $p=0.009$ and $t(68.2)=-2.006$, $p=0.049$; respectively] and a smaller PAS score reduction when compared with the SL genotype, but no difference when compared with the SS genotype [$t(65)=-2.167$, $p=0.034$ and $t(50)=-.013$, $p=0.98$; respectively].

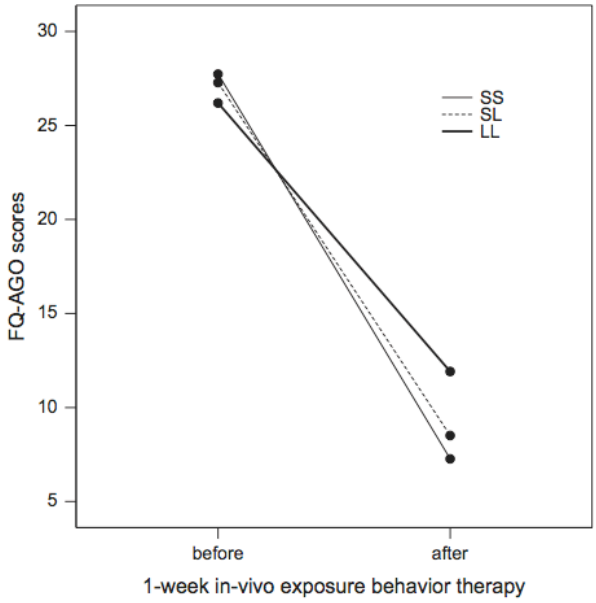

Fig. 1. The impact of 5-HTTLPR genotype on treatment response. FQ–AGO: Fear Questionnaire-agoraphobia subscale

Discussion

Intensive exposure-based behavior therapy strongly reduced the intensity of panic and avoidance (or PDA) symptoms as evidenced by a significant reduction on the FQ-AGO and PAS scores. Further, there was also a significant treatment X genotype

interaction effect. Patients with the LL genotype had a smaller FQ-AGO score reduction when compared with patients with the SS genotype and the SL genotype and a smaller PAS score reduction when compared with the SL genotype. As hypothesized, these findings show that the efficacy of exposure-based behavior therapy depends on the 5-HTTLPR polymorphism where PDA patients with the SS/SL genotype profit more as compared to patients with the LL genotype.

Table 1. Patient characteristics PDA. Panic disorder with Agoraphobia.

	SS (n = 24)	**SL (n = 41)**	**LL (n = 34)**	
Male	5 (21%)	8 (19.5%)	13 (38%)	X2 = 3.847; df = 2; p = 0.146
Female	19 (79%)	33 (80.5%)	21 (62%)	
Age (y)	36.8±10.3	38.8±11.9	41.1±13.7	F = 0.605; df = 2; p = 0.548
PDA duration (y)	10.9±9.2	12.1±12.0	12.7±11.6	F = 2.896; df = 2; p = 0.060
Antidepressant use	6	9	10	X2 = 0.131; df = 2; p = 0.936
Comorbid depression	8	12	10	X2 = 0.138; df = 2; p = 0.933
Comorbid specific phobia	6	8	6	X2 = 0.493; df = 2; p = 0.782

Table 2. Treatment response by 5-HTTLPR genotype. FQ-AGO: Fear Questionnaire-Agoraphobia Scale. MADRS: Montgomery-Asberg Depression Rating Scale. PAS: Panic and Agoraphobia Scale.

	SS		**SL**		**LL**	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
FQ-AGO	28.8±5.5	7.6±5.3	27.4±7.8	8.2±6.5	26.7±7.8	12.2±10.5
PAS	26.6± 7.7	11.0± 8.4	29.2±7.6	7.9± 7.1	29.9 ±7.7	14.4± 8.7
MADRS	12.9 ±7.3	8.1 ± 7.3	13.2± 7.2	9.0±7.7	14. 9±98.7	9.0± 6.9

Previous studies have looked into the relationship between the 5-HTTLPR and the success of different forms of cognitive behavioral therapy, showing mixed results. In one study, the SS-genotype was associated with a better treatment outcome (Eley et al., 2012). Subjects in this study were 584 children aged 6–13 years who received CBT for varied anxiety disorders. Successful treatment response was defined as the absence of an anxiety disorder at the end of the study. Twenty percent more children with the SS 5- HTTLPR genotype showed a favorable treatment response at 6-month follow-up, but not directly at post-treatment. In a study with only panic disorder patients (n = 69), the S/LG- allele of the 5-HTTLPR genotype (both bi-and tri-allelic) was associated with higher symptom severity prior to CBT but no association was found between genotype and the outcome of CBT (Lonsdorf et al., 2010). This lack of association between genotype and treatment success might be related to several issues. For instance the used outcome measure (HADS, Hospital Anxiety and Depression Scale) does not specifically measure panic symptoms or avoidance behavior due to panic attacks. Further, the use of two different CBT interventions (regular group and internet-based) could lead to a differential efficacy and therefore lack of power. In a study of 384 children with a primary anxiety disorder,

significant genetic, demographic and clinical predictors of outcome following CBT were identified (Hudson 2013). In predicting treatment outcome, six variables had a mini- mum mean beta value of 0.5 (5HTTLPR, NGF rs6330, gender, primary anxiety severity, comorbid mood disorder and comorbid externalizing disorder). A risk index constructed from these variables had moderate a predictive ability in this study. Children scoring high on this index were approxi- mately three times as likely to retain their primary anxiety disorder at follow-up as compared with low scoring children children. These results indicate that while in themselves functional polymorphisms appear to be insufficient to pre- dict therapy outcome, this does become feasible when combining them with clinical data. In the study of posttraumatic stress disorder, the effect of the 5-HTTLPR on the success of CBT (n = 45) has been examined as well, but here the L allele was associated with a more favorable outcome (Bryant et al., 2010). Fewer patients homozygous for the L-allele, compared to the S-allele carriers, met diagnostic criteria for PTSD at follow-up. It is noteworthy that immediately at the end of therapy, after 8 weeks of exposure-based CBT, no significant difference was found between genotypes. The difference only became apparent at 6-month follow-up, when the S-carriers seemed to relapse slightly whereas the L-carriers maintained their therapeutic effect. These genotype effects seen months after the delivery of CBT in the studies of Eley and Bryant suggests that other factors, apart from or only indirectly related to CBT, might be at play. The 5-HTTLPR appears to influence the success in which people cope with stressful life-events in general (Caspi et al., 2010; Caspi and Moffitt,2006; Caspi et al., 2003; Uher, 2009). It cannot be excluded that the effects of these studies are due to a general effect of the 5-HTTLPR on stress-sensitivity and coping, indirectly reflected in the improvement scores. The duration of the treatment described in the present study was only one week and the effects were measured shortly after. It is therefore more likely that these effects were due to the therapeutic intervention itself.

It is important to emphasize that the treatment in the present study consisted almost exclusively of exposure in vivo. This is different from the higher mentioned studies that employed a variety of techniques, albeit under the common denominator of CBT: imaginary exposure, exposure in vivo, cognitive restructuring, delivered via individual therapy, group therapy or Internet based therapy. As mentioned before, different aspects of therapy rely on different psychological processes and therefore likely also on differ- ent brain processes. The more varied psychological techni- ques are employed in a therapy, the more difficult it becomes to attribute the effect of genetic variation on the overall success of therapy to a particular technique and its supposed underlying biological mechanism. Exposure in vivo can be considered a form of extinction learning. Unfortunately however, direct experimental evidence (with extinction rate as outcome measure) for the effect of the 5-HTTLPR on extinction learning in humans is currently lacking (Lonsdorf and Kalisch, 2011; Lonsdorf et al., 2009). A separate line of gene-environment interaction research, that may partially reconcile these contrasting findings, provides direct support for the view that the low- expression form of the 5-HTTLPR gene is best regarded as a plasticity gene rather than a vulnerability gene (Belsky et al., 2009a; Belsky and Pluess, 2009b; Fox et al., 2011; Homberg and Lesch, 2011). In these studies, the S-allele increases sensitivity to the environment in a more general way; adverse environments lead to negative outcomes, and therefore may increase risk for psychopathology, while positive and supportive environments may ameliorate risk (Belsky et al., 2009a; Belsky and Pluess, 2009b; Uher, 2008). The environment

shapes the outcome of these fundamen- tally neutral common genetic factors (Uher, 2009) and it seems that there is a cost to the 'protective' L-allele since it may render less ability to maximize the potential of favorable situations (Belsky et al., 2009a; Homberg and Lesch, 2011; Uher, 2009). Several studies are compatible with the view that the 5-HTTLPR gene reflects environ- mental sensitivity. Fox et al. (2011) show that healthy individuals with the S-allele develop a stronger bias for both negative and positive affective pictures relative to those with L-allele of the 5-HTTLPR gene. Roiser et al. (2007) shows that in several studies the S-allele of the 5-HTTLPR gene is associated with improved cognitive functions.

Several limitations to our study need to be mentioned. First, although the sample size is among the largest of the studies into this subject focusing on a single anxiety disorder, it is still modest for a genetic study. This made for insufficient power to investigate other polymorphisms of interest that certainly exist. Especially the COMTVal158Met polymorphism, which is associated with poorer extinction learning as well as with CBT success in PDA, is worth investigating in future treatment studies (Lonsdorf and Kalisch, 2011). Second, some of the patients were taking an antidepressant. Hence, symptoms were still present in spite of medication. It is possible that there may be an overrepresentation of patients who did not respond well to the pharmacological treatment. However, no differences in medication status between the genotype groups were observed. Also, an effect of medication is rather unlikely given that patients were on a constant dosage for 2 months prior to inclusion. An additional effect of the medication on the PDA-symptoms after such a long period of time is not to be expected, but can never be ruled out (Bakker et al 2005). We therefore cannot completely exclude the possibility that medication status may have affected treatment outcome. Third, the outcome was measured shortly (2 weeks) after therapy. This design does not allow for evaluation of intermediate/long-term effects, as have been demonstrated in other therapy-genetic studies (Lonsdorf et al., 2010).

Our findings show that the 5-HTTLPR polymorphism may play a role in the response to exposure-based behavioral treatment in PDA. Overall, the 1-week intensive behavioral treatment dramatically reduced the intensity of agoraphobic symptoms in all patients. However, after therapy, those carrying the S-allele had agoraphobia scores compatible with complete remission, while L-carriers ended up with scores still compatible with mild agoraphobia (Mavissakalian, 1986; Roy-Byrne et al., 2005). These data support previous findings, indicating that genetic profiling might have a future role in identifying patients beforehand that require longer or more intensive psychological treatment.

References

Arias, B., Catalan, R., Gasto, C., Gutierrez, B., Fananas, L., 2003. 5-HTTLPR polymorphism of the serotonin transporter gene predicts non-remission in major depression patients treated with citalopram in a 12-weeks follow up study. Journal of clinical psychopharmacology 23, 563-567.

Bandelow, B., Brunner, E., Broocks, A., Beinroth, D., Hajak, G., Pralle, L., Ruther, E., 1998. The use of the Panic and Agoraphobia Scale in a clinical trial. Psychiatry research 77, 43-49.

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., Williams, R., 2009. Vulnerability genes or plasticity genes? Molecular psychiatry 14, 746-754.

Belsky, J., Pluess, M., 2009. Beyond diathesis stress: differential susceptibility to environmental influences. Psychological bulletin 135, 885-908.

Blaya, C., Salum, G.A., Lima, M.S., Leistner-Segal, S., Manfro, G.G., 2007. Lack of association between the Serotonin Transporter Promoter Polymorphism (5-HTTLPR) and Panic Disorder: a systematic review and meta-analysis. Behavioral and brain functions : BBF 3, 41.

Bryant, R.A., Felmingham, K.L., Falconer, E.M., Pe Benito, L., Dobson-Stone, C., Pierce, K.D., Schofield, P.R., 2010. Preliminary evidence of the short allele of the serotonin transporter gene predicting poor response to cognitive behavior therapy in posttraumatic stress disorder. Biological psychiatry 67, 1217-1219.

Caspi, A., Hariri, A.R., Holmes, A., Uher, R., Moffitt, T.E., 2010. Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. The American journal of psychiatry 167, 509-527.

Caspi, A., Moffitt, T.E., 2006. Gene-environment interactions in psychiatry: joining forces with neuroscience. Nature reviews. Neuroscience 7, 583-590.

Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., Poulton, R., 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301, 386-389.

Colasanti, A., Esquivel, G., den Boer, E., Horlings, A., Dandachi, A., Oostwegel, J.L., van Donkelaar, E.L., Griez, E.J., Schruers, K., 2011. Effects of tryptophan depletion and tryptophan loading on the affective response to high-dose CO2 challenge in healthy volunteers. Psychopharmacology 215, 739-748.

Eley, T.C., Hudson, J.L., Creswell, C., Tropeano, M., Lester, K.J., Cooper, P., Farmer, A., Lewis, C.M., Lyneham, H.J., Rapee, R.M., Uher, R., Zavos, H.M., Collier, D.A., 2012. Therapygenetics: the 5HTTLPR and response to psychological therapy. Molecular psychiatry 17, 236-237.

Feinn, R., Nellissery, M., Kranzler, H.R., 2005. Meta-analysis of the association of a functional serotonin transporter promoter polymorphism with alcohol dependence. American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics 133B, 79-84.

Fox, E., Zougkou, K., Ridgewell, A., Garner, K., 2011. The serotonin transporter gene alters sensitivity to attention bias modification: evidence for a plasticity gene. Biological psychiatry 70, 1049-1054.

Goossens, L., Sunaert, S., Peeters, R., Griez, E.J., Schruers, K.R., 2007. Amygdala hyperfunction in phobic fear normalizes after exposure. Biological psychiatry 62, 1119-1125.

Homberg, J.R., Lesch, K.P., 2011. Looking on the bright side of serotonin transporter gene variation. Biological psychiatry 69, 513-519.

Karg, K., Burmeister, M., Shedden, K., Sen, S., 2011. The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. Archives of general psychiatry 68, 444-454.

Keers, R., Aitchison, K.J., 2011. Pharmacogenetics of antidepressant response. Expert review of neurotherapeutics 11, 101-125.

Kim, W., Choi, Y.H., Yoon, K.S., Cho, D.Y., Pae, C.U., Woo, J.M., 2006. Tryptophan hydroxylase and serotonin transporter gene polymorphism does not affect the diagnosis, clinical features and treatment outcome of panic disorder in the Korean population. Progress in neuro-psychopharmacology & biological psychiatry 30, 1413-1418.

Linden, D.E., 2006. How psychotherapy changes the brain--the contribution of functional neuroimaging. Molecular psychiatry 11, 528-538.

Lonsdorf, T.B., Kalisch, R., 2011. A review on experimental and clinical genetic associations studies on fear conditioning, extinction and cognitive-behavioral treatment. Translational psychiatry 1, e41.

Lonsdorf, T.B., Ruck, C., Bergstrom, J., Andersson, G., Ohman, A., Lindefors, N., Schalling, M., 2010. The COMTval158met polymorphism is associated with symptom relief during exposure-based cognitive-behavioral treatment in panic disorder. BMC psychiatry 10, 99.

Lonsdorf, T.B., Weike, A.I., Nikamo, P., Schalling, M., Hamm, A.O., Ohman, A., 2009. Genetic gating of human fear learning and extinction: possible implications for gene-environment interaction in anxiety disorder. Psychological science 20, 198-206.

Marks, I.M., Mathews, A.M., 1979. Brief standard self-rating for phobic patients. Behaviour research and therapy 17, 263-267.

Mavissakalian, M., 1986. Clinically significant improvement in agoraphobia research. Behaviour research and therapy 24, 369-370.

Minelli, A., Bonvicini, C., Scassellati, C., Sartori, R., Gennarelli, M., 2011. The influence of psychiatric screening in healthy populations selection: a new study and meta-analysis of functional 5-HTTLPR and rs25531 polymorphisms and anxiety-related personality traits. BMC psychiatry 11, 50.

Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. The British journal of psychiatry : the journal of mental science 134, 382-389.

Munafo, M.R., Brown, S.M., Hariri, A.R., 2008. Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. Biological psychiatry 63, 852-857.

Pergamin-Hight, L., Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H., Bar-Haim, Y., 2012. Variations in the promoter region of the serotonin transporter gene and biased attention for emotional information: a meta-analysis. Biological psychiatry 71, 373-379.

Perna, G., Favaron, E., Di Bella, D., Bussi, R., Bellodi, L., 2005. Antipanic efficacy of paroxetine and polymorphism within the promoter of the serotonin transporter gene. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 30, 2230-2235.

Roffman, J.L., Marci, C.D., Glick, D.M., Dougherty, D.D., Rauch, S.L., 2005. Neuroimaging and the functional neuroanatomy of psychotherapy. Psychological medicine 35, 1385-1398.

Roiser, J.P., Muller, U., Clark, L., Sahakian, B.J., 2007. The effects of acute tryptophan depletion and serotonin transporter polymorphism on emotional processing in memory and attention. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum 10, 449-461.

Roy-Byrne, P.P., Craske, M.G., Stein, M.B., Sullivan, G., Bystritsky, A., Katon, W., Golinelli, D., Sherbourne, C.D., 2005. A randomized effectiveness trial of cognitive-behavioral therapy and medication for primary care panic disorder. Archives of general psychiatry 62, 290-298.

Schinka, J.A., 2005. Measurement scale does moderate the association between the serotonin transporter gene and trait anxiety: comments on Munafo et al. Molecular psychiatry 10, 892-893; author reply 895-897.

Schinka, J.A., Busch, R.M., Robichaux-Keene, N., 2004. A meta-analysis of the association between the serotonin transporter gene polymorphism (5-HTTLPR) and trait anxiety. Molecular psychiatry 9, 197-202.

Schruers, K., Esquivel, G., van Duinen, M., Wichers, M., Kenis, G., Colasanti, A., Knuts, I., Goossens, L., Jacobs, N., van Rozendaal, J., Smeets, H., van Os, J., Griez, E., 2011. Genetic moderation of CO2-induced fear by 5-HTTLPR genotype. Journal of psychopharmacology 25, 37-42.

Schruers, K., Griez, E., 2003. The effects of tryptophan depletion on mood and psychiatric symptoms. Journal of affective disorders 74, 305.

Schruers, K., Griez, E., 2004. The effects of tianeptine or paroxetine on 35% CO2 provoked panic in panic disorder. Journal of psychopharmacology 18, 553-558.

Schruers, K., Klaassen, T., Pols, H., Overbeek, T., Deutz, N.E., Griez, E., 2000. Effects of tryptophan depletion on carbon dioxide provoked panic in panic disorder patients. Psychiatry research 93, 179-187.

Schruers, K., van Diest, R., Overbeek, T., Griez, E., 2002. Acute L-5-hydroxytryptophan administration inhibits carbon dioxide-induced panic in panic disorder patients. Psychiatry research 113, 237-243.

Serretti, A., Calati, R., Mandelli, L., De Ronchi, D., 2006. Serotonin transporter gene variants and behavior: a comprehensive review. Current drug targets 7, 1659-1669.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of clinical psychiatry 59 Suppl 20, 22-33;quiz 34-57.

Taylor, M.J., Sen, S., Bhagwagar, Z., 2010. Antidepressant response and the serotonin transporter gene-linked polymorphic region. Biological psychiatry 68, 536-543.

Uher, R., 2008. The implications of gene-environment interactions in depression: will cause inform cure? Molecular psychiatry 13, 1070-1078.

Uher, R., 2009. The role of genetic variation in the causation of mental illness: an evolution-informed framework. Molecular psychiatry 14, 1072-1082.

Wendland, J.R., Martin, B.J., Kruse, M.R., Lesch, K.P., Murphy, D.L., 2006. Simultaneous genotyping of four functional loci of human SLC6A4, with a reappraisal of 5-HTTLPR and rs25531. Molecular psychiatry 11, 224-226.

Zanardi, R., Serretti, A., Rossini, D., Franchini, L., Cusin, C., Lattuada, E., Dotoli, D., Smeraldi, E., 2001. Factors affecting fluvoxamine antidepressant activity: influence of pindolol and 5-HTTLPR in delusional and nondelusional depression. Biological psychiatry 50, 323-330.

Chapter eight

General discussion

The aim in this thesis was to establish and understand the impact of gene and environmental factors on panic disorder while at the same time further our knowledge about factors that influence the effect of behavioral cognitive-therapy (CBT) in panic disorder (PD). To achieve this, first, CO2 inhalations were used as a model to provoke panic and smoking as a technique to enhance this panic provocation. Next, CBT was employed as a behavioral technique to gain insight in factors that determine the effect of psychological therapy in PD. Third, genetic techniques were used to explore a key neurotransmitter system and its relationship to PD symptom severity. The findings are discussed here and some concluding remarks are made.

Factors that influence panic

After experiencing a panic attack many PD patients start smoking more in an effort to avoid panic attacks ('self medication'). Smoking, however, seems to exacerbate rather than reduce panic symptoms. Since there is evidence supporting the idea that smoking can be anxiogenic but also anxiolytic, the question remains if 'smoking leads to panic' or 'panic leads to smoking' (**chapter 1**). In **chapter 3** and **chapter 4** we investigated the role of smoking in panic. **Chapter 3** describes an experimental study designed to test the 'panic' effects of smoking on the 35% CO2 challenge. Ninety-two patients (46 smokers and 46 non-smokers) with panic disorder and agoraphobia (PDA) were evaluated. The results show that PD smokers had a larger response to CO2 when compared to PD non-smokers. While baseline measures were similar in both groups, PD smokers reacted with more panic symptoms to the challenge. Fear scores showed the same effect, however without reaching statistical significance. In **chapter 4**, the literature regarding the comorbidity between cigarette smoking/nicotine dependence and panic (either panic attacks or panic disorder with or without agoraphobia) was surveyed. The aim was to achieve a broader perspective on the relationship between panic and cigarette smoking and to identify the possible underlying etiologic mechanisms. Twenty-four of the 61 studies screened met inclusion criteria. First, an overview of studies estimating the prevalence of the co-occurrence of cigarette smoking/nicotine dependence and panic attacks/panic disorder with or without agoraphobia was presented. Second, an overview of studies that examined the 3 causal models (from panic to smoking, from smoking to panic, and shared vulnerability) in turn was offered. Finally, experimental studies using laboratory panic provocation procedures were considered. These studies addressed the underlying mechanisms of the panic/ smoking link. Panic and cigarette smoking each appeared to have the capacity to serve as a causal factor in the development of the other. The bulk of the literature also supports a link between smoking and panic. The pathogenetic explanations of this co-occurrence referred mainly to 3 hypotheses. According to a moderational model, neuroticism is a third factor linking smoking to panic, as it moderates smoking frequency in subjects with a lifetime history of panic. According to a pathoplastic model of dysfunction, smoking acts as a vulnerability factor that modifies the expression of panic disorder by exacerbating affective disturbances and negative health processes. Finally, in line with the false suffocation alarm theory, smoking, by means of increasing the risk of lung disease or impacting the carotid body, may reduce the threshold to suffocation signals and indirectly increase the risk of panic. The first 2 hypotheses have been supported by several studies. A few studies found a

unidirectional relationship going from smoking to panic. Only one study showed a bidirectional relationship between smoking and panic. In experimental work almost all studies have found that cigarette smoking increases fear reactivity to a biological challenge, both in panic disorder patients as in healthy volunteers. In studies evaluating patients with nicotine dependence, it was found that the more severe the level of nicotine dependence, the higher the risk of comorbidity with panic.

Previous literature has clearly shown the large extent of a comorbid depressive disorder in PD patients. Literature also suggests that a concurrent depressive disorder may also influence the severity of the panic symptoms. A large body of evidence has documented that the effects of cognitive behavioral therapy (CBT) for the treatment of panic disorder are robust and durable. With regard to CBT, some evidence suggests that a concurrent depressive disorder influences the treatment outcome for manualized behavioral therapy for PDA. Furthermore, CBT focussing on the panic disorder, may also improve the concurrent depressive symptoms (**chapter 1**). **Chapter 6** describes a study examining the relationship of comorbid depression on treatment outcome for manualized behavioral therapy for PDA in a large group of outpatients. It was found that both depressed and non-depressed PDA patients profit from CBT focused on the PDA, which is in line with most recent studies. Although the comorbidity group had significantly higher scores on the anxiety scales (PAS, FQA) at baseline, there were no significant differences at post-treatment between groups. Both groups improved significantly during therapy with a reduction of more than 70% on initial scores on the PAS and a reduction of more than 67% on initial scores on the FQA. In the depressed group the FQA score was reduced from severe agoraphobia at baseline to agoraphobia in remission at post-treatment and in the non-depressed group from severe agoraphobia at baseline to agoraphobia in remission at post-treatment. The present study also confirmed that manualized behavioral treatment focusing on PDA also effectively reduces depressive symptomatology as measured by the MADRS, which is also in line with previous studies. Although the depressed PDA patients still scored significantly higher at post-treatment on the MADRS than did the non-depressed PDA patients, there was a significant effect of treatment on the depressive symptoms in both groups.

Although the extent of the contribution of genetics versus environmental factors on PD is still not clearly defined, we cannot rule out an important role of genetics in PD. Some studies suggest that genes also play a role in treatment outcome following behavior therapy (**chapter 1**). **Chapter 5** shows a relationship between the 5-HTT-linked polymorphic region (5-HTTLPR) genotype and the response to exposure-based behavior therapy in patients with PDA. Ninety-nine patients with PDA underwent a 1-week in-vivo exposure-based behavior therapy program and were classified according to their 5-HTTLPR genotype. It was found that intensive exposure-based therapy reduced measures of panic and avoidance (or PDA) symptoms as evidenced by a significant reduction on the FQ-AGO and PAS scores. Furthermore, there was a significant treatment by genotype interaction effect. Patients with the LL-genotype had smaller FQ-AGO reductions when compared with patients with the SS-genotype and the SL-genotype and smaller PAS reductions when compared with the SL-genotype.

Clinical relevance

Since the work in this thesis has established that cigarette smoking has the tendency to promote panic itself (**chapter 3** and **chapter 4**), quitting smoking might prevent relapse in panic symptoms. Therefore, smoking cessation interventions should be added to the general treatment plan of the smoking PD patient.

Based on the current literature, CBT is the first choice in the treatment for panic disorder and exposure in vivo is indicated if agoraphobia is present. Many studies show that 'short-term CBT', this is 12 weekly sessions of CBT, is effective in treating PD (**chapter 1**). In an effort to think about cost-effectiveness of treatments and also to make CBT available to more patients, offering CGT in a more high-density format could be a solution. The question is if a 12-week CBT program is necessary to treat PD successfully or can this program be intensified. In **chapter 5**, the results of a study that tested the efficacy of an intensive 1-week behavioral therapy program focusing on agoraphobia for PDA patients are is reported. The main outcome measure was the agoraphobia score of the Fear Questionnaire (FQ-AGO). The outcomes on the FQ- AGO after a 1-week intensive therapy (96 patients) and a twice-weekly therapy (98 patients) were compared. It was found that agoraphobia improved significantly in both groups, 1 week and 3 months after therapy, respectively. This study shows that a 1-week CBT program for PD patients with severe agoraphobia was as successful as the classical 12 'weekly' CBT format, allowing PD patients to return faster to work and to recapture their daily activities. The more rapid reduction of symptoms is not only an advantage for the individual, but it also has economic benefits for the community. Since modified CBT, like intensified therapy, proves to be as effective as the standard therapies, it can be offered to a broader population of patients with panic disorder. Intensified CBT would for example be useful for patients who cannot attend the standard 12 weekly sessions because of practical problems such as lack of child care, transportation, financial resources or scheduling conflicts with working hours.

Since a comorbid depressive disorder in PD does not appear to affect the outcome of CBT focusing on PD negatively and moreover, the depressive symptomatology is reduced 'spontaneously' (**chapter 6**), it seems possible to treat both psychiatric disorders at the same time without modifying the therapeutic plan of treating PD. Treating the panic disorder seems to have beneficial effects on the depressive disorder, and therefore it would be more cost effective to treat the principal disorder, PD, instead of to spend extra time and means to treat each disorder separately. The high co- occurrence of these two mental disorders, and the knowledge that panic disorder usually precedes the onset of the depressive disorder, makes that PD patients should be carefully checked for the presence of a depressive disorder. However, it is recommendable to assess both disorders consistently disregarding the initial reason for consultation. Since our sample is directly derived from an outpatient setting, patients on medication and patients with all kind of comorbidity were included. Therefore, the characteristics of the patients can be considered as typical for PD patients in an outpatient setting. The naturalistic nature of the study ensures that our results are relevant for daily clinical practice. In **chapter 5** we showed that PD patients carrying the S- allele of the 5-HTTLPR polymorphism had a better response to the 1-week intensive behavioral treatment CBT program than S- allele carriers.

When editing the individualized therapy program of the individual with PD at the start of the treatment, genetic profiling could be considered since L- allele carriers might demand a longer or more intensive treatment.

Future research

The finding that cigarette smoking has the tendency to promote panic itself is consistent with previous research that cigarette smoking appears to be a causal link in the development of PD. Smoking also seems to precede the onset of panic, however reviewing the literature, the relation to time is still under debate. The etiopathogenetic explanations of this co-occurrence are also still being discussed. The following studies can maybe shed light into this temporal pattern and the underlying mechanisms: (1) epidemiologic studies involving new samples, (2) epidemiologic and clinical studies with attention for the gender, (3) clinical studies comparing the link between smoking and other anxiety disorders with the relationship between smoking and panic (4) experimental studies carried out in sovereign labs and (5) replication of research focusing on mutual vulnerability. Furthermore, trials illuminating the link between certain lifestyles, such as regular exercise, and panic disorder could contribute to optimizing treatment of PD. Smoking however, should be considered as a substance use disorder rather than a lifestyle or habit, as a standardized use of the diagnosis of nicotine dependence will benefit the diagnostic evaluation and will be helpful in comparing studies.

Since cost-effectiveness of treatment is a major topic in health care, the finding that a 1-week CBT program for PD patients with severe agoraphobia was as successful as the classical 12 'weekly' CBT format, is important. Further examining the possibilities to shorten the duration of therapy is crucial.

Clinical trials investigating the effect of high-density therapy, which means several hours of therapy within a few days, and also other modified forms of CBT (for example internet-based CBT) are needed since they also increase the accessibility of CBT. One of the limitations in comparing studies examining the effectiveness of CBT, which consist of multiple aspects, is the difficulty to determine which components are responsible for producing favorable outcomes. Studies disentangling CBT in his different components would be very valuable since 'straight- forwarded' interventions can lead to a faster reduction of the panic symptoms.

Since the treatment for panic disorder is delivered in the 'real world', and concurrent mental disorders are the rule and not the exception, studies examining the effectiveness of different approaches for PD, should include comorbidity in an attempt to complete the findings of rigorously controlled efficacy trials. Only if the characteristics of the participants are clear, this can lead to defining the optimal pathways and approaches in treating PD across the variety of settings (e.g. primary care, tertiary settings)

To date, little research is available about the genetic factors that can predict response on CBT in PD. Studies aiming to identify genes that are associated with response to CBT, or other therapies, could lead to a more tailored approach and in time maybe to personalized medicine. More knowledge in this field would also help to identify the individuals more at risk for the disorder. To gain more insight in the

complex, non-Mendelian, traits of PD, association studies, using candidate genes, are promising.

Defining genes that increase susceptibility to panic disorder and delineating genes that interact with known environmental risk factors such as smoking, could also help in optimizing and developing current and new treatments in PD.

In general, studies defining the characteristics that can predict positive response to a known psychological or pharmacological PD treatment are needed. These 'predictors' could help the psychiatrist in choosing the most effective treatment for that specific individual with PD.

Since 70% of the (succesfully) treated PD patients keep on having some degree of panic symptoms over the course of several years, more research is needed to evaluate long-term effectiveness and to individualize and optimize relapse prevention strategies. A clear definition of relapse and remission is needed. Most studies address only short- term outcomes, leaving many questions concerning relapse unanswered. Studies including follow- up periods of several years are needed in order to get more insight into factors and treatments that can help to maintain remission.

Chapter nine

Valorization

Societal need

The twelve month prevalence of PD is estimated around 1% and the lifetime prevalence rates range from 1,5 to 4,7 % (Mendlowiz and Stein, 2000; Norton et al., 2008; Pane – Farre et al., 2014). As described elsewhere in this thesis (see the introduction), panic disorder can lead to substantial human suffering and dysfunction (e.g. Wittchen et al., 1998; Alonso et al., 2004a; Kessler et al., 2006) and also to a high economic strain on society (Katon et al., 2002; Zaubler and Katon, 1998). If not treated, there is a real chance that panic disorder becomes a chronic, very disabling disease.

Data regarding the cost of panic disorder are particularly relevant since panic disorder is frequently left untreated; at least half the patients with panic disorder do not get help (Wang et al., 2005; Leon et al., 1995), but can potentially be treated successfully (van Balkom et al., 1997; Bakker et al., 2002). By reducing both medical (also non-psychiatric) expenses and production losses (Magruder and Calderone, 2000), treating panic disorder more efficiently is likely economically worthwhile.

Like in every disorder or illness, the costs associated with panic disorder can be divided into direct medical costs, direct non-medical costs and indirect costs associated with the specific morbidity.

Direct medical costs consist of treatment costs generated by a wide scope of health services including the prescription of drugs. Direct non-medical costs consist of expenses that arise when people travel to health service providers (Oostenbrink et al., 2004). Indirect non-medical costs caused by panic disorder consist of costs due to the loss of paid labor and decreased functioning in personal life.

The nature of the symptoms of panic disorder, often accompanied with avoidance behavior (Weissman et al., 1997), is inherently connected with higher costs; a lot of physical symptoms leading to the wrong diagnosis, often followed by referral to the wrong service (Harvison et al., 2004), excess impairment (Kessler et al., 2005; Alonso et al., 2004a; Kouzis and Eaton, 2000), unfavorable natural course (Eaton et al., 1998; Robins et al., 1991; Wittchen, 1988). Moreover, these cost increasing factors often lead to absenteeism from work and work cutback days (Alonso et al, 2004a). Further, comorbidity of panic disorder with other mental disorders (Alonso et al., 2004b) is frequent and adds further to the costs. As panic disorder affects many people (Kessler et al., 2005), the cost for the community is substantial.

Cost of illness studies performed in the Netherlands, have done an attempt to calculate the economic impact of panic disorder on society (Batelaan et al., 2007; Smit et al., 2006) and to compare the economic cost of panic disorder with other mental disorders. These data were derived from a prospective psychiatric epidemiologic survey that was conducted in the adult general population of the Netherlands (Bijl et al., 1998).

Smit et al. (2006) showed that the estimated annual costs per patient ('per- capita costs') suffering from panic disorder (with or without agoraphobia) were €13,894. At least three quarters of costs were due to loss of production whereas direct non-medical costs only accounted for a limited fraction (less then 10%) of total costs. The

study also showed that panic disorder generated €226 million costs per one million inhabitants annually ('the costs on societal level'). At population level, the costs generated by panic disorder were both in the same range of costs generated by major depressive disorder and dysthymia combined and also in the same range of costs generated by generalized anxiety disorder, social phobia and simple phobia combined.

As expected, comorbidity increased costs (Jacobi et al., 2004; Knerer et al., 2005) but since only one fourth of the annual per capita costs was attributable to the concurrent mental disorder, this effect was moderate.

It is important to realize that this is a conservative cost estimation since the span of the study of Batelaan et al. (2007) was narrowed to the year 2003. The costs over a longer time, such as mortality costs and costs generated by secondary disorders, were therefore not included. Previous studies however suggest that these costs in the long run might be substantial in panic disorder (Goodwin et al., 2004; Greenberg et al., 1999). Since service use and work loss days were assessed retrospective by self-reports, and decreased productivity while at work ('work cut-back') can be substantial (Greenberg et al., 1999; Kessler and Frank, 1997; Lim et al., 2000) but could not be measured for obvious reasons, there is a real chance that these outcomes are also an underestimation. A considerable cost that is also not accounted for in this estimation are the frequent visits to various (non-psychiatric) medical specialists and emergency departments (Leon et al., 1997; Rees et al., 1998; Greenberg et al.,1999).

Since PD is associated with multiple physical symptoms and the intensity of these symptoms is often mistaken for a life-threatening physical illness such as a heart attack, PD patients often visit emergency rooms where they often receive extensive and very costly medical check-ups (Katon et al., 2002; Zaubler and Katon,1998).

Although the total medical cost will increase following adequate treatment (Andrews et al., 2004; Salvador-Carulla et al.,1995), the production 'gain' after treatment will reduce the overall societal costs and will improve the quality of life of the individual significantly (Salvador-Carulla et al., 1995). So, given the present low treatment rate for panic disorder (Wang et al., 2005), increased treatment coverage would lead to a substantial reduction of the societal costs.

On the basis of these data, we can conclude that both the costs per individual as the societal costs of panic are substantial, that the loss of production seems the biggest part of the costs and that panic disorder is one of the most costly common mental disorders. Consequently, panic disorder should be regarded as a public health problem with great economic consequences.

In a time that cost- effectiveness is the 'keyword' in health care, further studies focusing on health economics, both on individual and on societal level, are warranted. Especially studies based on the general population are important since they have 'access' to the costs of all panic patients regardless of whether they received treatment. If we would only focus on treatment samples (e.g. Rees et al., 1998), we would overlook a substantial part of the costs since at least half the subjects with panic do not receive help (Wang et al., 2005; Leon et al., 1997). Although these patients generate fewer costs in health care, they may generate substantial costs due to absenteeism from work. The company doctor is therefore a

key player in the early detection of patients with a panic disorder. Also, map-ping the medical costs associated with the visits to numerous (non-psychiatric) medical specialists and emergency departments is a necessity. Further studies are also needed to verify whether improved 'patient-finding' followed by providing treatment according to the evidence-based guidelines of panic disorder, would indeed reduce the economic costs to society.

Although the resources are limited and efforts to limit costs are needed, the constant pressure to treat patients ''shorter and quicker' in order to increase the 'production', is nowadays enormous in mental health. If studies show that a specific therapy can be limited in time, for instance if intensified, this does not automatically mean that every therapist is capable of performing this therapy; know-how and expertise are essential. Constantly cutting on costs in mental health has its limits since it threatens working according to the evidence-based guidelines and therefore quality of care.

Target groups

First of all, panic patients should benefit from the results of this thesis. Smoking cessation might be a strategy in the prevention of, or preventing relapse in, panic symptoms. The duration of cognitive behavioral therapy focusing on panic disorder with agoraphobia (PDA), could be shortened, if intensified, and this could have several benefits for the patients; easier access to therapy, a more rapid reduction of symptoms and thus a more rapid return to work and resumption of daily activities. PDA patients with a comorbid major depression can be treated for the depression and PDA at the same clinic.

General practitioners, company doctors, (non–psychiatric) medical specialists (such as the cardiologist, pulmonologist and emergency doctor) but also psychiatrists and mental health workers in general, should be informed about the high prevalence and the heterogeneous symptomatology of PD and be aware of their important role in especially the early detection of the PD patient. Since the public authorities decide how to divide the resources in mental health, they should be informed about the (economical) impact of PD on society.

Activities/ Products/ Innovation

Informing the general public about the symptoms and extent of PD is essential. Many panic patients are embarrassed, feel 'weird' and different, and therefore wait many years before telling the general practitioner about their complaints. Involving patient organizations can help to educate the general population. Personal stories in popular media like women's magazines often help patients to make the first step. Publishing in more general medical journals (also Dutch papers) and lectures for general practitioners and company doctors, will lead to more knowledge about PD. Working closer together with the medical (non- psychiatric) specialists in the general hospitals can prevent medical shopping as they play a key role in the (early) detection of PD.

The application of our results in the Academic Anxiety Center, is the first step in an effort to replicate our results and extend our knowledge of PD; introducing a smoking cessation program as part of treatment strategy in PD, further explora-tion of strategies to shorten the duration of therapies focusing on PD, treating PD patients with comorbid major depression the same as PD patients with no comorbidity and systematically collecting DNA samples from PD patients in an attempt to develop in time a more personalized treatment protocol according to the patient's genetic profile.

Since the exact underlying pathophysiology of panic remains largely unknown, more knowledge on the genetic determinants and the environmental factors that play a role in panic is necessary. The use of the 35% CO2 challenge can be considered as a good experimental model for panic and can therefore be used in order to get more insight in the underlying pathophysiology of panic disorder with the aim of earlier detection of PD. Using CO2 challenges in translational research, imaging, and genetic research, will extend our knowledge on PD and maybe even lead to prevention strategies of PD. CO2 challenges are already used in treatment of PD as interoceptive exposure and therefore can help to develop better treatment strategies.

Collaboration with other research groups, also international, is since many years an important topic at the Academic Anxiety Centre. Also teaching medical (non-psychiatrists and psychiatrists) specialists from other hospitals to perform CO2-challenges is part of spreading the know-how of PD. In order to develop better and more adjusted equipment to perform CO2 challenges, and to make the equipment available to other research groups but also clinical settings, there has been already collaboration with "Maastricht Instruments".

Employing acquired skills within network

Writing this thesis, I learned the steps of research; formulating a hypothesis, writing the protocol for a study to substantiate such a hypothesis, organizing carefully the practical matters, collecting data, 'looking' at data to understand what they say, making statistical analyses and writing papers. Furthermore, I learned the techniques of the 35% CO2 - challenge. The combination of clinical work, management tasks, teaching and performing research activities created the opportunity for collaboration at several levels between clinical and research groups.

References

Alonso, J., Angermeyer, M.C., Bernert, S., Bruffaerts, R., Brugha, T.S., Bryson, H., Girolamo, G., de Graaf, R., Demyttenaere, K., Gasquet, I., Haro, J.M., Katz, S.J., Kessler, R.C., Kovess, V., Lepine, J.P., Ormel, J., Polidori, G., Russo, L.J., Vilagut, G., Almansa, J., Arbabzadeh-Bouchez, S., Autonell, J., Bernal, M., Buist-Bouwman, M.A., Codony, M., Domingo-Salvany, A., Ferrer, M., Joo, S.S., Martinez-Alonso, M., Matschinger, H., Mazzi, F., Morgan, Z., Morosini, P., Palacin, C., Romera, B., Taub, N., Vollebergh, W.A., 2004a. Disability and quality of life impact of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (EseMeD) project. Acta Psychiatr Scand. 109(Suppl 420), 38-46.

Alonso, J., Angermeyer, M.C., Bernert, S., Bruffaerts, R., Brugha, T.S., Bryson, H., Girolamo, G., de Graaf, R., Demyttenaere, K., Gasquet, I., Haro, J.M., Katz, S.J., Kessler, R.C., Kovess, V., Lepine, J.P., Ormel, J., Polidori, G., Russo, L.J., Vilagut, G., Almansa, J., Arbabzadeh-Bouchez, S., Autonell, J., Bernal, M., Buist-Bouwman, M.A., Codony, M., Domingo-Salvany, A., Ferrer, M., Joo, S.S., Martinez-Alonso, M., Matschinger, H., Mazzi, F., Morgan, Z., Morosini, P., Palacin, C., Romera, B., Taub, N., Vollebergh, W.A., 2004b. 12-Month comorbidity patterns and associated factors in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand. 109(Suppl 420), 28-37.

Andrews, G., Issakidis, C., Sanderson, K., Corry, J., Lapsley, H., 2004. Utilising survey data to inform public policy: comparison of the cost-effectiveness of treatment of ten mental disorders. Br J Psychiatry. 184, 526-533.

Bakker, A., van Balkom, A.J.L.M., Spinhoven, P., 2002. SSRIs vs. TCAs in the treatment of panic disorder: a meta-analysis. Acta Psychiatr Scand. 106(3), 163- 167.

Batelaan, N., de Graaf, R., van Balkom, A., Vollebergh, W., Beekman, A., 2007. Thresholds for health and thresholds for illness: panic disorder versus subthreshold panic disorder. Psych Med. 37, 247 – 256.

Bijl, R.V., van Zessen, G., Ravelli, A., de Rijk, C., Langendoen Y., 1998. The Netherlands Mental Health Survey and Incidence Study (NEMESIS): objectives and design. Soc Psychiatry Psychiatr Epidemiol. 33, 581-586.

Eaton, W.W., Anthony, J.C., Romanoski, A., Tien, A., Gallo, J., Cai, G., Neufeld, K., Schlaepfer, T., Laugharne, J., Chen, L.S., 1998. Onset and recovery from panic disorder in the Baltimore Epidemiologic Catchment Area follow-up. Br J Psychiatry. 173, 501-507.

Goodwin, R.D., Lieb, R., Hoefler, M., Pfister, H., Bittner, A., Beesdo, K., Wittchen, H.U., 2004. Panic attack as a risk factor for severe psychopathology. Am J Psychiatry. 161, 2207-2214.

Greenberg, P.E., Sisitsky, T., Kessler, R.C., Finkelstein, S.N., Berndt, E.R., Davidson, J.R.T., Ballenger, J.C., Fyer, A.J., 1999. The economic burden of anxiety disorders in the 1990s. J Clin Psychiatry. 60, 427-435.

Harvison, K.W., Woodruff-Borden, J., Jeffery, S.E., 2004. Mismanagement of panic disorder in emergency departments: Contributors, costs, and implications for integrated models of care. J Clin Psychol Med. S11, 217-232.

Jacobi, F., Wittchen, H.U., Hölting, C., Höfler, M., Pfister, H., Müller, N., Lieb, R., 2004. Prevalence, co-morbidity and correlates of mental disorders in the general population: results from the German Health Interview and Examination Survey (GHS). Psychol Med. 34, 597-611.

Katon WJ, Roy-Byrne P, Russo J, Cowley D: Cost- effectiveness and cost offset of a collaborative care intervention for primary care patients with panic disorder. Arch Gen Psychiatry 2002; 59:1098– 1104

Kessler, R.C., Chiu, W.T., Demler, O., Merikangas, K.R., Walters, E.E., 2005. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 62, 617-627.

Kessler, R. C., Chiu, W. T., Jin, R., Ruscio, A. M., Shear, K., Walters, E. E., 2006. The epidemiology of panic attacks, panic disorder, and agoraphobia in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 63, 415-424.

Kessler, R.C., Frank, R.G., 1997. The impact of psychiatric disorders on work loss days. Psychol Med. 27, 861-873.

Knerer, G., Byford, S., Johnson, T., Seivewright, H., Tyrer, P., 2005. The Nottingham study of neurotic disorder: predictors of 12 year costs. Acta Psychiatr Scand. 112, 224-232.

Kouzis, A.C., Eaton W.W., 2000. Psychopathology and the initiation of disability payments. Psychiatr Serv. 51, 908-913.

Leon, A.C., Olfson, M., Portera, L., 1997. Service utilization and expenditures for the treatment of panic disorder. Gen Hosp Psychiatry. 19, 82-88.

Leon, A.C., Portera, L., Weissman, M.M., 1995. The social costs of anxiety disorders. Br J Psychiatry. 166(Suppl 27), 19-22.

Lim, D., Sanderson, K., Andrews, G., 2000. Lost productivity among full-time workers with mental disorders. J Ment Health Policy Econ. 3, 139-146.

Magruder, K.M., Calderone, G.E., 2000. Public health consequences of different thresholds for the diagnosis of mental disorders. Comprehensive Psychiatry. 41, 14-18.

Mendlowicz, M.D. and Murray B.Stein, M.D. Quality of life in Individuals With Anxiety Disorders. Am J Psychiatry 2000; 157:669-682.

Norton, P.J., Zvolensky, M.J., Bonn-Miller, M.O., Cox, B.J., Norton, G.R., 2008. Use of the Panic Attack Questionnaire-IV to assess non-clinical panic attacks and limited symptom panic attacks in student and community samples. J Anxiety Disord 22, 1159-1171.

Oostenbrink, J.B., Bouwmans, C.A.M., Koopmanschap, M.A., 2004. Manual for Costing: Methods and standard costs for economic evaluations in health care (Dutch). College voor zorgverzekeringen, Diemen, the Netherlands.

Pane-Farre, C.A., Stender, J.P., Fenske, K., Deckert, J., Reif, A., John, U., Schmidt, C.O., Schulz, A., Lang, T., Alpers, G.W., Kircher, T., Vossbeck-Elsebusch, A.N., Grabe, H.J., Hamm, A.O., 2014. The phenomenology of the first panic attack in clinical and community-based samples. J Anxiety Disord 28, 522-529.

Rees, C.S., Richards, J.C., Smith, L.M., 1998. Medical utilisation and costs in panic disorder: a comparison with social phobia. J Anxiety Disord. 12, 421-435.

Robins, L.N., Locke, B.Z., Regier, D.A., 1991. An overview of psychiatric disorders in America. In: Robins, L.N. and Regier, D.A.(Eds), Psychiatric disorders in America : the Epidemiological Catchment Area Study. The Free Press, a division of Macmillian, New York, pp 328-366.

Salvador-Carulla, L., Segui, J., Fernandez-Cano, P., 1995. Costs and offset effect in panic disorders. Br J Psychiatry. 166, 23-28.

Smit, F., Cuijpers, P., Oostenbrink, J., Batelaan, N., de Graaf, R., Beekman, A., 2006. Costs of common mental disorders: implications for curative and preventive psychiatry. J Ment Health Policy Econ. 9, 193 – 200.

van Balkom, A.J.L.M., Bakker, A., Spinhoven, P., Blaauw, B., Smeenk, S., Ruesink, B., 1997. A meta analysis of the treatment of panic disorder with or without agoraphobia: A comparison of psychopharmacological, cognitive behavioral and combination treatment. J Nerv Ment Dis. 185, 510-516.

Wang, P.S., Lane, M., Olfson, M., Pincus, H.A., Wells, K.B., Kessler, R.C., 2005. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. Arch Gen Psychiatry. 62, 629-640.

Weissman, M.M., Bland, R.C., Canino, G.J., Faravelli, C., Greenwald, S., Hwu, H.G., Joyce, P.R., Karam, E.G., Lee, C.K., Lellouch, J., Lepine, J.P., Newman, S.C., Oakley-Browne, M.A., Rubio-Stipec, M., Wells, J.E., Wickramaratne, P.J., Wittchen, H.U., Yeh, E.K., 1997. The cross-national epidemiology of panic disorder. Arch Gen Psychiatry. 54, 305-309.

Wittchen, H.U., Nelson, C.B., Lachner, G., 1998. Prevalence of mental disorders and psychosocial impairments in adolescents and young adults. Psychol Med. 28, 109-126.

Wittchen, H.U., 1988. Natural course and spontaneous remissions of untreated anxiety disorders results of the Munich follow-up study (MFS). In: Hand, I. and Wittchen, H.U. (Eds), Panic and Phobias 2. Treatments and Variables Affecting Course and Outcome. Springer-Verlag, Berlin, Germany, pp 3-17.

Zaubler, T.S., Katon, W., 1998. Panic disorder in the general medical setting. Journal of Psychosomatic Research 44:25-42

Chapter ten

Epilogue

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SUMMARY

The introduction in **chapter 1** illustrates the daily life of a patient with panic disorder (PD). The case report includes the clinical presentation, diagnostic evaluation, psychometric evaluation, the use of the CO2 challenge and the choice of treatment. Also, the diagnostic 'tools', the implications for the individual and society, the factors that have an influence on PD and the different ways to treat PD are described.

Chapter 2 gives a general overview of the studies performed in this thesis. The aim of this thesis was to establish and explain the impact of gene and environmental factors on panic disorder. At the same time, the objective was to extend our knowledge about factors that have an impact on the effect of cognitive-behavioral therapy (CBT) in panic disorder (PD).

To get more insight in the environmental factors that influence panic, CO2 inhalations were used as a model to provoke panic and smoking as a technique to enhance this panic provocation. **Chapter 3** describes an experimental study constructed to investigate the 'panic' effects of smoking on the 35% CO2 challenge. While baseline measures were similar in both groups, the 46 PD smokers reacted with more panic symptoms to the challenge when compared to the 46 PD non-smokers. Fear scores showed the same effect, but without reaching statistical significance. These results suggest that smoking facilitates 35% CO2 acute 'panic' effects in PD patients and support the hypothesis that prior regular smoking increases the risk for panic attacks in PD patients.

The literature regarding the comorbidity between cigarette smoking/nicotine dependence and panic (either panic attacks or panic disorder with or without agoraphobia) was reviewed in **chapter 4**. The intention of the review was to achieve a wider picture on the relationship between panic and cigarette smoking and to determine the potential underlying etiologic mechanisms. The studies that were included were divided into 3 categories; studies estimating the prevalence of the co-occurrence of cigarette smoking/nicotine dependence and panic attacks/panic disorder (with or without agoraphobia), studies that examined the 3 causal models (from panic to smoking, from smoking to panic, and shared vulnerability) and experimental studies using laboratory panic provocation procedures and so addressing the underlying mechanisms of the panic/smoking link. The bulk of the literature supports a link between smoking and panic and each appeared to have the capacity to serve as a causal factor in the development of the other. The pathogenetic explanations of this co-occurrence referred mainly to 3 hypotheses; neuroticism links smoking to panic as it moderates smoking frequency in subjects with a lifetime history of panic ('the moderational model'), smoking acts as a vulnerability factor that modifies the expression of panic disorder by exacerbating affective disturbances and negative health processes ('the pathoplastic model of dysfunction'), smoking, by means of increasing the risk of lung disease or impacting the carotid body, may reduce the threshold to suffocation signals and indirectly increase the risk of panic ('the false suffocation alarm theory'). The first 2 hypotheses

have been supported by several studies. A few studies found a unidirectional relationship going from smoking to panic, whereas only one study showed a bidirectional relationship between smoking and panic. In studies evaluating patients with nicotine dependence, it was found that the more severe the level of nicotine dependence, the higher the risk of comorbidity with panic. In experimental studies almost all studies have found that cigarette-smoking increases fear reactivity to a biological challenge, both in panic disorder patients as in healthy volunteers. The overall conclusion is that panic and cigarette smoking each appear to have the capacity to serve as a causal factor/facilitator in the development of the other. Although the temporal pattern and the pathogenetic explanations of such a co-occurrence are still a matter of debate, cigarette smoking tends to precede the onset of panic and to promote panic itself.

In **chapter 5**, **chapter 6** and **chapter 7**, CBT were used as a behavioral technique to gain insight in factors that determine the effect of therapy in PD. In **chapter 5** the efficacy of an intensive 1-week behavioral therapy program focusing on agoraphobia for PDA patients was examined. The outcomes on the agoraphobia score of the Fear Questionnaire (FQA), FQA as the main outcome measure, were compared after a 1-week intensive therapy (96 patients) and a twice-weekly therapy (98 patients). Agoraphobia was found to improve significantly in both groups, 1 week and 3 months after therapy, respectively. These findings suggest that behavioral therapy for agoraphobia can be shortened if intensified without affecting therapy outcome.

In **chapter 6**, the results of a study in a large group of outpatients examining the relationship of comorbid depression on treatment outcome for manualized behavioral therapy for PDA, are described. In line with most recent studies, the study shows that both depressed and non-depressed PDA patients profit from CBT focused on the PDA. Both groups improved significantly during therapy with a reduction of more than 70% on initial scores on the PAS and a reduction of more than 67% on initial scores on the FQA. In the depressed group the FQA score was reduced from severe agoraphobia at baseline to agoraphobia in remission at post-treatment and in the non-depressed group from severe agoraphobia at baseline to agoraphobia in remission at post-treatment. Although the comorbidity group had significantly higher scores on the anxiety scales (PAS, FQA) at baseline, there were no significant differences at post-treatment between groups. Also in line with previous studies, the present study confirmed that manualized behavioral treatment focusing on PDA also effectively reduces depressive symptomatology as measured by the MADRS. There was a significant effect of treatment on the depressive symptoms in both groups, although the depressed PDA patients still scored significantly higher at post-treatment on the MADRS than did the non-depressed PDA patients Together, these data suggest that comorbid depressive disorder is not a 'drawback' to treatment response and successful treatment of panic disorder is associated with reductions of comorbid depressive symptoms.

In **chapter 7**, genetic techniques were used to explore key neurotransmitter systems and surveyed PD patients on their symptom severity. In this study, 99 patients with PDA underwent a 1-week in-vivo exposure-based behavior therapy program and

were classified according to their 5- HTTLPR genotype. It was found that the LL-genotype had smaller FQA reductions when compared with patients with the SS-genotype and the SL-genotype and smaller PAS reductions when compared with the SL-genotype.

Since there was a significant treatment by genotype interaction effect, the results show a relationship between the 5-HTT-linked polymorphic region (5-HTTLPR) genotype and the response to exposure-based behavior therapy in patients with PDA. These findings reveal that the efficacy of exposure-based behavior therapy is related to 5-HTTLPR polymorphism where PDA patients with the SS/SL-genotype show a larger response when compared to patients with the LL genotype. This study suggests a genetic factor in treatment outcome following behavior therapy and implicates the serotonergic system in response to CBT in PDA.

In the general discussion in **chapter 8** the results of the studies in this thesis are discussed with regard for the environmental and genetic factors that influence panic and CBT and the clinical relevance of the results. Also, some concluding remarks for future research are made.

In **chapter 9** ('Valorization') the social and economic relevance, the target groups to whom (and why) the results are of interest, the activities/ products and the innovative nature of the studies performed, are described.

SAMENVATTING

De introductie in **hoofdstuk 1** beschrijft het dagelijks leven van een patiënt met een paniekstoornis. De casus bevat de klinische presentatie, de diagnostische en psychometrische evaluatie, het gebruik van de CO2 challenge en de behandeling. Ook worden diagnostische handvatten, factoren die een invloed hebben op de paniekstoornis en de verschillende mogelijkheden van behandeling van een paniekstoornis beschreven.

Hoofdstuk 2 geeft een algemeen overzicht van de studies die werden uitgevoerd in kader van dit proefschrift. Het doel van het proefschrift was om de impact van genetische en omgevingsfactoren op de paniekstoornis te bevestigen en verklaren. Een ander streven was om de kennis over de factoren die een invloed hebben op cognitieve gedragstherapie in de behandeling van de paniekstoornis uit te breiden.

Om meer inzicht te krijgen in de omgevingsfactoren die paniek beïnvloeden, werden CO2 inhalaties gebruikt als een model om paniek op te wekken en roken als een techniek om de paniekreactie te vergroten. In **hoofdstuk 3** wordt een experimentele studie beschreven die het 'paniekeffect' van roken op de CO2 challenge onderzoekt. Hoewel in beide groepen de basismetingen gelijk waren, reageerden de 46 rokers met een paniekstoornis met meer paniek-symptomen op de challenge dan de 46 niet-rokers met een paniekstoornis. De vrees- scores toonden hetzelfde effect maar dit verschil was niet statistisch significant. Deze resultaten suggereren dat roken het 35% CO2 acute 'paniekeffect' faciliteert bij patiënten met een paniekstoornis en ondersteunt de hypothese dat voorafgaand regelmatig roken het risico op een paniekaanval doet toenemen bij patiënten met een paniekstoornis.

De literatuur betreffende de comorbiditeit tussen sigaretten roken/ nicotine afhankelijkheid en paniek (paniekaanvallen of paniekstoornis met of zonder agorafobie) werd besproken in **hoofdstuk 4**. De opzet van de review was om een beter zicht te krijgen op de relatie tussen paniek en roken enerzijds en de mogelijk onderliggende etiologische mechanismen anderzijds. De studies die geïncludeerd werden, werden verdeeld in 3 categorieën: de studies die een schatting maakten van de prevalentie van de gelijktijdige aanwezigheid ('co- occurrence') van roken / nicotine afhankelijkheid en paniekaanvallen/ paniekstoornis (met of zonder agorafobie), de studies die de 3 causale modellen onderzochten (van paniek naar roken, van roken naar paniek, en gedeelde kwetsbaarheid) en tenslotte de experimentele studies. Bij deze laatste werd gebruik gemaakt van procedures die een paniek-reactie kunnen opwekken in een laboratorium om zo de onderliggende mechanismen van het verband tussen paniek en roken te achterhalen. Het grootste deel van de literatuur ondersteunt een link tussen roken en paniek waarbij beide het vermogen lijken te hebben om als causale factor te kunnen dienen in de ontwikkeling van de andere. De pathogenetische verklaringen van deze 'co-occurrence' refereren hoofdzakelijk naar 3 hypotheses. Neuroticisme 'linkt' roken aan paniek omdat het een invloed heeft op de frequentie van roken in patiënten met een voorgeschiedenis van paniek ('the moderational model'). Roken kan ook

beschouwd worden als een kwetsbaarheidsfactor die de uiting van de paniekstoornis wijzigt door het verergeren van affectieve ontregelingen en negatieve gezondheidsprocessen ('the pathoplastic model of dysfunction'). Tenslotte kan roken het risico op longaandoeningen vergroten of rechtstreeks een invloed uitoefenen op de carotis lichaampjes en zo de drempel voor verstikkingssignalen verlagen, waardoor indirect het risico op paniek toeneemt ('the false suffocation alarm theory'). De eerste 2 hypotheses werden onder-steund door verschillende onderzoeken. Enkele onderzoeken vonden een unidirectioneel verband van roken naar paniek, terwijl maar één onderzoek een bidirectioneel verband aantoonde tussen roken en paniek. In onderzoeken die patiënten met een nicotine afhankelijkheid onderzochten, werd aangetoond dat hoe groter de afhankelijkheid van nicotine is, hoe hoger het risico is op comorbiditeit met paniek. In experimentele onderzoeken hebben bijna alle studies aangetoond dat roken de 'vrees reactiviteit' doet toenemen als reactie op een biologische challenge en dit zowel in patiënten met een paniekstoornis als in gezonde vrijwilligers. De algemene conclusie is dat paniek en sigaretten roken elk het vermogen lijken te hebben om te dienen als causale factor / facilitator in de ontwikkeling van de andere. Hoewel het tijdsverloop en de pathogenetische verklaringen van een dergelijke 'co-occurrence' nog steeds het voorwerp van discussie zijn, lijkt het dat roken het begin van de paniekstoornis vooraf gaat en paniek zelf bevordert.

In **hoofdstuk 5**, **hoofdstuk 6** en **hoofdstuk 7**, werd cognitieve gedragstherapie (CGT) gebruikt als een techniek om inzicht te krijgen in de factoren die het effect van therapie bepalen bij de paniekstoornis. In hoofdstuk 5 werd onderzocht hoe effectief CGT, gericht op agorafobie, is als CGT als een intensief ('1- week') programma wordt gegeven bij patiënten met een paniekstoornis. De uitkomsten van de agorafobie score van de Fear Questionnaire (FQA) als de belangrijkste uitkomstmaat werden vergeleken na een 1 week intensief programma (98 patiënten) versus een twee- wekelijkse therapie (98 patiënten). De mate van agorafobie nam significant af in beide groepen en dit respectievelijk 1 week en 3 maanden na therapie. Deze bevindingen suggereren dat de duur van het geven van gedragstherapie gericht op agorafobie korter kan indien de therapie intensiever wordt gegeven en dit zonder het resultaat van de behandeling te beïnvloeden.

In **hoofdstuk 6** worden de resultaten beschreven van een onderzoek in een grote groep ambulante patiënten waarin de relatie van een comorbide depressieve stoornis op de behandeluitkomst van gedragstherapie voor paniekstoornis wordt onderzocht. In overeenstemming met de meest recente studies, toont dit onderzoek aan dat zowel depressieve als niet- depressieve patiënten met een paniekstoornis met agorafobie baat hebben van CGT die gericht is op de paniekstoornis met agorafobie. Beide groepen verbeterden significant tijdens therapie met een afname van meer dan 70% van de PAS –scores en een afname van meer dan 67% van de FQA- scores ten opzichte van de scores bij het begin van de behandeling. De FQA- scores in de depressieve groep namen af van ernstige agorafobie bij start van de behandeling naar agorafobie in remissie na de behandeling. De FQA-scores in de niet-depressieve groep namen af van ernstige agorafobie bij start van de behandeling naar agorafobie in remissie na de behandeling.

Hoewel de depressieve groep bij start van de behandeling significant hogere scores had op de angst- schalen (PAS, FQA), waren er na de behandeling geen significante verschillen tussen de 2 groepen. In overeenstemming met eerdere studies, bevestigt dit onderzoek dat op behandelrichtlijnen gebaseerde gedragstherapie gericht op de paniekstoornis met agorafobie ook doeltreffend de depressieve symptomen reduceert. Er was een significant effect van behandeling op de depressieve symptomen in beide groepen hoewel de depressieve patiënten na de behandeling wel nog steeds significant hoger scoorden op de MADRS dan de niet – depressieve patiënten. Deze data geven aan dat een comorbide depressieve stoornis geen nadeel is voor de behandeluitkomst en dat succesvolle behandeling van de paniekstoornis geassocieerd is met een afname van de comorbide depressieve symptomen.

In **hoofdstuk 7** werden genetische technieken gebruikt om fundamentele neurotransmittor systemen te onderzoeken en de ernst van de symptomen van patiënten met een paniekstoornis na te gaan. In dit onderzoek volgden 99 patiënten met een paniekstoornis met agorafobie een 1-week in-vivo exposure-gericht CGT programma en werden de patiënten geclassificeerd volgens hun 5-HTTLPR genotype. Het onderzoek toonde aan dat patiënten met het LL-genotype een kleinere afname hadden van de FQA- en PAS- scores in vergelijking met de patiënten met het SS- en het SL-genotype. Gezien er een significant 'treatment x genotype interaction' effect was, tonen de resultaten een verband tussen het 5-HTT-linked polymorphic region (5-HTTLPR) genotype en het effect van de exposure-gerichte gedragstherapie in patiënten met een paniekstoornis met agorafobie. Deze bevindingen onthullen dat het effect van exposure- gerichte gedragstherapie verbonden is aan het 5-HTTLPR polymorfisme en dat patiënten met een paniekstoornis met agorafobie die het SS/SL-genotype hebben een groter effect ondervinden van therapie in vergelijking met patiënten met het LL genotype. Dit onderzoek suggereert dat een genetische factor een invloed heeft op de uitkomst van gedragstherapie en impliceert dat het serotonerge systeem een rol speelt in de CGT bij patiënten met een paniekstoornis met agorafobie.

In de algemene discussie in **hoofdstuk 8** worden de resultaten van het onderzoek in dit proefschrift besproken met aandacht voor de omgevings- en genetische factoren die paniek en CGT beïnvloeden en het klinische belang van de resultaten. Ook worden er enkele afsluitende voorstellen gedaan voor toekomstig onderzoek.

In **hoofdstuk 9** ('Valorization') wordt het sociale en economische belang, de doelgroepen voor wie de resultaten van de gedane onderzoeken van belang zijn (en waarom), de activiteiten/ produkten en het innovatieve van de onderzoeken beschreven.

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Nu het proefschrift af is, en mama terug 'naar huis' komt, gaan we veel meer tijd samen hebben! Ixtapa, we komen eraan!

CURRICULUM VITAE

Inge Knuts werd geboren op 13 juni 1972 in Hasselt, België. Na de lagere school te Wimmertingen, doorliep ze de middelbare school aan de Humaniora Virga Jesse te Hasselt, richting Latijn-wiskunde- fysica. De kandidaturen geneeskunde volgde ze aan het Limburgs Universitair Centrum (LUC) te Diepenbeek en ze voltooide haar studies geneeskunde aan de Katholieke Universiteit Leuven (KUL) waar ze in 1997 met onderscheiding het diploma van arts behaalde. Na een aanvullende opleiding (eerste deel) Criminologie aan de KUL, startte ze in 1998 met de opleiding tot psychiater in Leuven (Kortenberg) waar ze in 2003 het getuigschrift van geneesheer specialist in de psychiatrie behaalde. In 2004 behaalde ze het universitair postgraduaatdiploma cognitieve gedragstherapie aan het Universitair Ziekenhuis te Antwerpen. Van februari 2004 tot mei 2015 was ze werkzaam als psychiater bij de Mondriaan (aanvankelijk PMS Vijverdal) in Maastricht. Over de jaren heen werkte ze als psychiater op de afdeling NAH, poli NAH, poli ADHD en poli ASS. Van 2006 tot 2014 werkte ze ook als psychiater op het Academisch Angstcentrum (AAC) te Maastricht en dit in combinatie met een promotietraject. Van 2011 tot en met 2014 werkte ze tevens als manager zorg op de poli's ADHD en ASS op de locaties Maastricht en Heerlen. Daarnaast had ze over de jaren verspreid ook enkele onderwijstaken aan de Universtiteit Maastricht en behaalde ze het certificaat van deelname aan de cursussen (zomer en winter) van de master in Affective Neuroscience (Universiteit van Firenze en Maastricht). Sinds 1 mei 2015 is ze werkzaam als psychiater in België.

LIST OF PUBLICATIONS

I. Knuts, C. Baeken, H. D'haenen (1999). Paniekstoornis. Medi-sfeer, nummer 96

I. Knuts, H. D'haenen (2000). De nieuwe antidepressiva. Medi-sfeer, nummer 113

I. Knuts, H. D'haenen (2003). Complexe psychiatrische symptomatologie als begin van multiple sclerose. Tijdschrift voor Psychiatrie,

Knuts IJ, Cosci F, Esquivel G, Goossens L, van Duinen M, Bareman M, Overbeek T, Griez EJ, Schruers KR (2010). Cigarette smoking and 35% CO2 induced panic in panic disorder patients. J Affect Disord 124(1-2):215-8.

Knuts I, Esquivel G, Kenis G, Overbeek T, Leibold N, Goossens L, Schruers K (2014). Therapygenetics: 5-HTTLPR genotype predicts the response to exposure therapy for agoraphobia'. Eur Neuropsychopharmacol. Volume 24, Issue 8, Pages 1222–1228

Inge JE Knuts, Gabriel Esquivel ,Thea Overbeek, Koen RJ Schruers (2015). Intensive behavioral therapy for agoraphobia. Journal of Affective Disorders Volume 174, Pages 19–22

Knuts I, Esquivel G, Overbeek T, and Schruers K. The effect of depressive symptoms on behavioral treatment for panic disorder with agoraphobia (in press).

Fiammetta Cosci, **Inge Knuts**, Kenneth Abrams, Eric JL Griez, Koen RJ Schruers (2010). Cigarette smoking and panic. A critical review of the literature. J Clin Psychiatry, 71(5):606–615

Esquivel G, Dandachi A, **Knuts I**, Goossens L, Griez E, Schruers K (2012). Effects of acute exercise on CO2 -induced fear. Depress Anxiety, 29(2): 155-8.

Schutters SI, Viechtbauer W, **Knuts IJ**, Griez EJ, Schruers KR (2012). 35% CO2 sensitivity in social anxiety disorder. J Psychopharmacol.J Psychopharmacol, 26(4): 479-86.

Schruers K, Esquivel G, van Duinen M, Wichers M, Kenis G, Colasanti A, **Knuts I**, Goossens L, Jacobs N, van Rozendaal J, Smeets H, van Os J, Griez E (2011). Genetic moderation of CO2-induced fear by 5-HTTLPR genotype. J Psychopharmacol, 25(1):37-42

Goossens L, Leibold N, Peeters R, Esquivel G, **Knuts I**, Backes W, Marcelis M, Hofman P, Griez E, Schruers K (2014). Brainstem response to hypercapnia: A symptom provocation study into the pathophysiology of panic disorder. J Psychopharmacol 28(5):449-56.

‘Every new beginning comes from some other beginning’s end’ (Seneca)