MASTERTHESIS

A Holistic Model of the Relation Between Panic Disorder and Fatigue

Conducting a Systematic Review of Etiology, Maintenance, and Treatment

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'[…] treatable panic disorder is an important contributor […] to the etiology and clinical presentation of chronic fatigue […].'

(Manu, Matthew, & Lane, 1991, p.451)

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Abstract

In this thesis, a systematic literature review that aims to deliver a comprehensive overview on the interdependent relation between Panic Disorder (PD) and fatigue is conducted. Special attention is paid to etiological processes, maintaining factors and treatment concepts for PD patients that experience fatigue.

Background and Objective. PD as well as fatigue have a great detrimental impact on an affected person's life. Up to date, research on the mutual influence these two constructs have on each other is still insufficient. As a starting point for the explorative data search, the first impression of the relation between panic disorder and fatigue was illustrated in an 'etiological model of panic disorder and fatigue'.

Method. The systematic literature review was conducted in spring 2017. In order to examine the relation between PD and fatigue, journal articles were retrieved from five scientific databases. After three phases of screening, N = 16 articles were included into the final data pool by combining the key term 'PD' with various search terms for 'fatigue' and by relating to etiology, maintenance, and treatment.

Results. The literature review revealed that sleep characteristics, sleep duration and Nocturnal Panic Attacks contribute to the etiology of fatigue in PD patients. Besides, fatigue has found to be maintained by a vicious cycle of dysfunctional beliefs, cognitive biases, safety behaviour, and increased sleep effort. With regard to the treatment of PD patients who experience fatigue, it was found that fatigue and sleep related complaints are side effects in PD medication. The conventional treatment combination for PD patients consisting of Cognitive Behavioural Therapy and medication is ascertained to be unsatisfactory when intending to achieve improvements in PD patients that undergo fatigue and related symptoms.

Conclusion. The main findings of the conducted review indicated to expand and adjust the 'etiological model of panic disorder and fatigue'. The resulting 'holistic model of the relation between panic disorder and fatigue' can be seen as the first attempt to visualize the relation between PD and fatigue. Further, it can be seen as the starting basis for further exploration of the influence of PD as well as fatigue on the mutual etiology, maintenance, and treatment concepts of PD as the relevant and fatigue as the secondary diagnosis.

Keywords: panic disorder, fatigue, etiology, maintenance, treatment

Kurzfassung

In dieser Abschlussarbeit wurde eine systematische Literaturrecherche durchgeführt, um einen umfassenden Überblick über den Zusammenhang zwischen Panikstörung und Müdigkeit zu erstellen. Den Ausgangspunkt für die explorative Literatursuche bildete das ‚ätiologische Modell der Panikstörung und Müdigkeit', welches basierend auf dem einem Eindruck von der Beziehung zwischen Panikstörung und Müdigkeit erstellt wurde.

Hintergrund und Zielsetzung. Sowohl Panikstörung als auch Müdigkeit haben erhebliche negative Auswirkungen auf die Lebensqualität Betroffener. Bis heute mangelt es an ausreichender Forschung hinsichtlich des gegenseitigen Einflusses beider Erscheinungsformen. Daher zielt diese Studie darauf ab, wissenschaftliche Erkenntnisse über die Beziehung zwischen Panikstörung und Müdigkeit zu erheben. Diese könnten insofern einen Beitrag zu künftigen Behandlungsmöglichkeiten von Panikpatienten liefern, als dass gleichzeitig auftretende Müdigkeitsbeschwerden zusätzlich behandelt werden könnten.

Methodik. Die systematische Literaturrecherche wurde im Frühjahr 2017 durchgeführt. Um die wechselseitige Beziehung zwischen Panikstörung und Müdigkeit deutlich zu machen, wurden Journalartikel aus fünf wissenschaftlichen Datenbanken zusammengestellt. Durch die Kombination des Schlüsselbegriffs ‚Panikstörung' mit differenzierten Suchbegriffen zum Thema Müdigkeit als auch in Bezug auf die Ätiologie, Aufrechterhaltung und Behandlungsmöglichkeiten, konnten nach drei systematischen Screeningphasen N=16 Artikel im endgültigen Datenpool zusammengestellt werden.

Resultate. Die Literaturrecherche ergab, dass Schlafcharakteristiken, Schlafdauer und nächtliche Panikattacken zum Entstehen von Müdigkeit bei Panikpatienten beitragen. Außerdem konnte festgestellt werden, dass Müdigkeit bei Panikpatienten durch einen Teufelskreis bestehend aus dysfunktionalen Überzeugungen, Sicherheitsverhalten und erhöhtem Schlafaufwand aufrechterhalten wird. Im Hinblick auf die Behandlung von Panikpatienten, die unter Müdigkeit leiden, wurde festgestellt, dass Müdigkeit und schlafbedingte Beschwerden häufig als Nebenwirkungen von Psychopharmaka zur Behandlung von Panikstörungen auftreten. Die konventionelle Behandlungskombination für Panikpatienten, bestehend aus kognitiver Verhaltenstherapie und Medikation, wird als unzureichend bewertet, wenn es darum geht Verbesserungen in Bezug auf Müdigkeitsbeschwerden bei Panikpatienten zu erzielen.

Fazit. Die wichtigsten Ergebnisse der durchgeführten Literaturüberprüfung ermöglichten eine Erweiterung und Anpassung des ätiologischen Modelles der Panikstörung und Müdigkeit. Das daraus resultierende "ganzheitliche Modell der Beziehung zwischen

Panikstörung und Müdigkeit" kann als erster Versuch angesehen werden, die Beziehung zwischen Panikstörung und Müdigkeit zu visualisieren. Das Modell sollte außerdem als Ausgangspunkt für die weitere Erforschung des gegenseitigen Einflusses von Panikstörung und Müdigkeit genutzt werden.

Schlüsselbegriffe: Panikstörung, Müdigkeit, Ätiologie, Aufrechterhaltung, Behandlung

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Introduction

Relevance

Being afflicted with fatigue and related symptoms has significant detrimental effects on a person's mood and coping resources, leading to a lower life quality and hence, to an increased vulnerability to develop comorbid psychiatric diseases as affective and somatoform disorders (Harvey, Wesseley, Kuh, & Hotopf, 2009). Compared to current research concerning the relation of fatigue and physical diseases, only a few of the published articles cover the relation between fatigue and particular psychiatric diseases such as anxiety disorders has been published. More particularly, only few studies are concerned with the relation between panic disorder (PD) and fatigue. The necessity to fill in this research gap is facilitated by the severity and high prevalence of both phenomena causing detrimental effects on daily functioning and the quality of life of concerned people (Barton, Karner, Salih, Baldwin, & Edwards, 2014). By now, no reviews that explicitly assess the relation between PD and fatigue, have been published. This systematic literature review aims to give a comprehensive overview of the relation between both phenomena by considering relevant issues such as etiology, maintenance, and treatment concepts.

Panic Disorder

Definition of Panic Disorder. PD, a key concept in this review, is a mental disease, corresponding to the DSM-IV classification of anxiety disorders (American Psychiatric Association, 1994). People suffering from PD experience unexpected panic attacks mostly independent from specific situations or objects. Panic attacks are spontaneous episodes of intense fear. When being in the given episode, people undergo an accelerated heart rate, sweating, dizziness, and numbness among other symptoms. Moreover, concerns about the recurrence of panic attacks and corresponding consequences are prevalent in between such episodes (Barton, Karner, Salih, Baldwin, & Edwards, 2014). According to the DSM-IV classification, PD commonly emerges with the presence or absence of agoraphobia, which is an extensive fear triggered by being in particular situations or places. According to Grant, Hasin, Stinson, Dawson, Goldberg et al. (2006), the occurrence of PD with agoraphobia has proved to be a more severe variant of PD. In the DSM-V (updated 2013), the diagnosis of agoraphobia is independent of the diagnosis of PD (American Psychiatric Association, 2013).

Etiology and Maintenance of Panic Disorder. PD has psychological as well as biological causes. To illustrate the etiology of PD and the underlying mind-body relation, four crucial aspects, based on Emmelkamp, Bouman, and Visser (2009) are displayed in a holistic model (see Figure 1). In a first approach to explain the development of PD, Emmelkamp et al. (2009), mention *heritability*, which is found to explain the development of PD in about 48%. Concerned people often inherit the predisposition to develop PD. Although evidence is found for possible deviations in physiological systems of PD patients, as an impaired respiratory center or lower heartrate variability once PD is diagnosed, these findings were not replicated and conclusions based on this evidence should be made with caution. Next to physiological

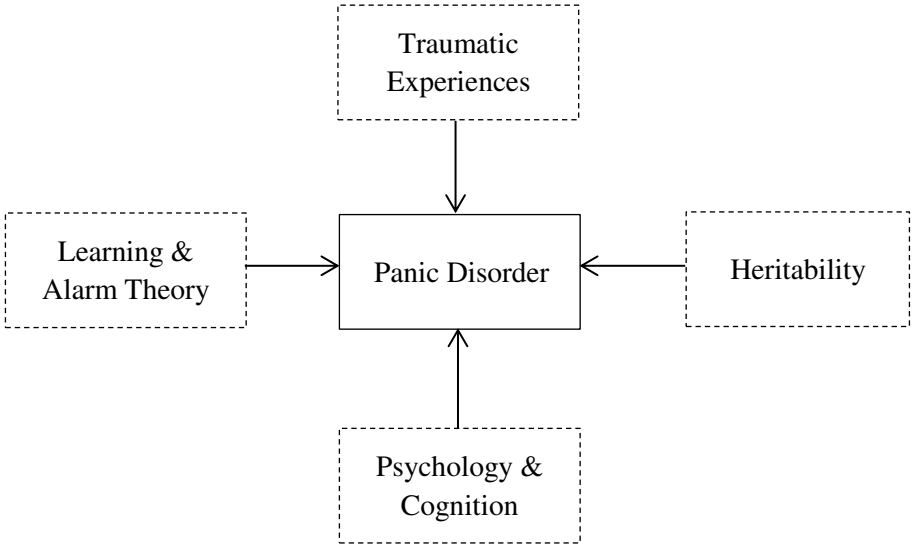

Figure 1. Holistic model of the etiology of panic disorder.

aspects Emmelkamp et al. (2009) emphasize the crucial role of *psychological and cognitive aspects* in the development and maintenance of PD. PD patients commonly misinterpret bodily sensations as signs of catastrophes, leading to increased anxiety. This attentional bias can be explained by the activation of latent interoceptive anxiety. Interoceptive anxiety means, that PD patients evaluate their current state of anxiety on the basis of bodily sensations instead of external signs or information. Thus, if strong anxiety is provoked, this hidden (latent) interoceptive anxiety is activated and PD patients experiences extensive fear. Another theory, resting upon the physiological theory described, is the *learning/ alarm theory*. Learning theory assumes that an inherent alarm system warns the individual in case of danger. It further emphasizes the impact of interoceptive conditioning, which assumes that every physical sensation will lead to a panic attack. As a result, anxiety sensibility, or fear of fear is

developed. As a last approach, Emmelkamp, Bouman, and Visser (2009) mention the finding that *early traumatic experiences* increase the chance for the development of PDs.

How close mind and body are related in the nature of PD becomes clear again after having a closer look at the maintenance of PD. According to Ehlers (1995), maintenance and relapse depend on an individual's heartbeat perception, anxiety sensibility, avoidance patterns and safety-seeking behavior. Great safety-seeking behavior is found to increase catastrophic beliefs and anxiety (Salkovskis, Clark, Hackmann, Wells, & Gelder, 1999). Moreover, baseline levels of anxiety severity, comorbidity and previous mental disorders account for present maintenance of PD. Finally, the type of PD treatment and its success is another contributor to the maintenance of PD symptoms.

Treatment of Panic Disorder. The instant need to treat PD by medical services is emphasized by Katon (1996), who states that patients commonly seek help when suffering from somatic symptoms associated with PD. According to Emmelkamp et al. (2009), PD can be treated by applying the methods of three treatment approaches. First, *cognitive change* has to be made. This could be done by Cognitive Therapy, which focuses on bringing change in the individual's catastrophic misinterpretations. Secondly, *behavioral change* has to be targeted in effective treatment of PD. The individual is challenged to not apply safety behavior by the use of verbal or behavioral techniques. Thirdly, by learning *coping strategies* the patient learns to deal with bodily sensations that commonly provoke a panic attack. Panic attacks can be decreased by means of systematic interoceptive exposure, a treatment in which PD patients are exposed to their feared bodily sensations over a prolonged time. Research has shown that a combination of the three described treatment approaches, commonly known as Cognitive Behavioral Therapy (CBT), is most appropriate to treat PD patients as it causes a decrease of panic attacks, anxiety, and avoidance (Otto, Pollack, & Sebatino, 1996).
Next to the therapeutic approach, another option to improve panic symptoms is *pharmacological therapy.* Tricyclic antidepressants, SSRI's, SNRI's and benzodiazepines are proven to be effective. In case of acute episodes of PD, it is recommended to combine Cognitive Therapy and medication. Moreover, group treatments are found to be more effective than single-person treatment. Overall, PD patients are commonly and most effective treated with a combination of CBT and pharmacological therapy.

Comorbidity and Prevalence of Panic Disorder. Diagnosing and treating PD requires considering mental and physical comorbidities. According to De Jonge et al. (2016), PD has a great comorbidity with mood disorders (bipolar disorder), impulse-control disorders (binge eating disorder and bulimia nervosa), as with substance- use disorders. This gives an indication of the incidence of PD. The NEMESIS-2 study, which assessed the incidence of psychiatric disorders in the Netherlands have found a lifetime prevalence of PD of 3.8%. The 12 – months prevalence in the Netherlands has found to be 2.2% (Trimbos Instituut, 2012). A comparable study has been assessed by the Robert- Koch Institut in Germany. The German population has shown a one-year prevalence of 3.0% in women, and 1.7% in men (Robert Koch- Institut, 2002). Overall, the probability to suffer from PD is found to be two times higher in females than in males (Angst et al., 2016). Furthermore, there is a higher prevalence rate of PD in high-income countries than in low-income countries. Additionally, lifetime comorbidity in people suffering from PD was about 80.4%. These numbers indicate what the NEMESIS study has shown- anxiety disorders are equally prevalent as mood disorders on a lifetime basis what emphasizes the need to conduct research on anxiety disorders as PD.

Fatigue

Definition of Fatigue. Due to its complexity, there is no consensus definition of fatigue. Yet, four definitions of fatigue are presented in the following to make clear how fatigue, which is a key concept in this review, is understood in this paper. In scientific literature, fatigue is often defined in terms of dualistic concepts. First, normal fatigue is distinguished from pathological fatigue. The definition relies on the duration of experiencing fatigue and on the nature of recovery. *Normal, acute fatigue* is often a consequence of short-term sleep loss or exhaustive mental or physical work. It occurs in healthy individuals who commonly recover rapidly after taking a rest. P*athological, chronic fatigue* occurs in patients with severe mental and physical illness. A characteristic of pathological, chronic fatigue is that the fatigue symptoms last over long time periods and are difficult to restore, which can lead to enormous consequences for the patients daily life functioning. Secondly, physical fatigue is distinguished from psychological fatigue. *Physical fatigue* relies on bodily activity and energy loss or consumption. This matches the behavioral viewpoint on fatigue, which also says that an individual that experiences fatigue and related symptoms commonly lacks energy, which causes a decline in the individual's activity level and a disturbance on an individual's (daily) performance (Shen, Barbera, & Shapiro, 2006). In contrast, *psychological fatigue*

originates from high stress levels, low motivation levels, and weariness, which may cause depressive or anxiety symptoms. The most severe manifestation of psychological fatigue is the CFS. This syndrome is a pathological, severe mental illness a patient can have as a main diagnose. The decisive difference between CFS and fatigue is that fatigue is not a main diagnose. Thus, CFS is not considered in this review. The paper solely focuses on all forms of fatigue defined above.

To give a comprehensive understanding of fatigue, the difference with sleepiness has to be presented. Research has found that fatigue is commonly related to sleepiness (Shen, Barbera, & Shapiro, 2006). Both phenomena are described as separate, but interrelated appearances. According to Shen, Barbera, and Shapiro (2006), sleepiness can be distinguished from fatigue due to the extent of impairment of the normal arousal level, considering that fatigue impairs the arousal level to a greater extent. Sleepiness is defined as one's tendency to fall asleep (sleep propensity). Although fatigue and sleepiness are associated, this paper aims to differentiate between both and to consider merely fatigue. Thus, this review targets all forms of fatigue by excluding CFS and sleepiness.

Risk Factors, Comorbidity, and Prevalence of Fatigue. Due to the multidimensionality of fatigue and related symptoms, a number of factors account for its high prevalence (Shen et al., 2006). Theorell-Haglow, Lindberg, and Janson (2006) identified risk factors for fatigue and daytime sleepiness for women. First of all, it is found that the risk to experience symptoms of fatigue and sleepiness increases with age. Secondly, lifestyle factors play a central role in the etiology of daytime sleepiness and fatigue. Examples that facilitate fatigue are physical inactivity and smoking. Moreover, short sleep duration, and insomnia serve as predictors for fatigue and sleepiness in woman (Theorell-Haglow, Lindberg, & Janson, 2006). Thirdly, as mentioned above, comorbidity with several chronic and acute physical and mental diseases strongly increases the risk to develop fatigue and sleepiness. Among others, frequent comorbidities are found with rheumatoid arthritis, cancer, snoring and being overweight, as with experiencing psychological distresses like anxiety and depression.

The great range of comorbidities fatigue entails already suggests the detrimental effects fatigue and sleepiness have on a person's general health and quality of life. According to Shen, Barbera, and Shapiro (2006), fatigue is even '[…] identified as major debilitating and even life-threatening factor in working populations.' (p. 67). The symptoms and consequences of fatigue are still overlooked and underestimated in the diagnose and treatment of comorbid physical and mental diseases although its prevalence is considerable.

Theorell- Haglow, Lindberg and Janson (2006) report an estimated prevalence of fatigue and day time sleepiness of 5.5% to 23% in the general population, while women are found to suffer from fatigue more often than men. Additionally, Kroenke, and Price (1993) found a lifetime prevalence of fatigue lasting for two or more weeks in 20% of the US population.

Panic Disorder and Fatigue

When having a closer look at the nature of PD and fatigue, it is obvious that both of them have mainly contrasting symptoms (DSM-IV). While PD causes an accelerated heart rate, sweating, and intense fear among others, fatigue is characterized by exhaustion and lack of vitality. Furthermore, fatigue is not listed as a symptom of PD. Thus, both do not seem to relate to each other at first. Nevertheless, research has shown a co-occurrence of PD and fatigue. Galligan, Hevey, Coen, and Harbison (2015) found a significant relation between both constructs in patients who recovered from stroke. Furthermore, Manu, Matthews, and Lane (1991) found an enhanced probability to develop a PD when suffering from extensive fatigue previously. Up to date, no research was found stressing out the etiology and relation of PD and fatigue when co-occurring. To demonstrate the first impression concerning relations between PD and fatigue based on the recent literature, a hypothetic, etiological model of panic disorder and fatigue (see Figure 2) is created.

The ‘etiological model of panic disorder and fatigue’ displays the assumed relation between the emergence of panic attacks, that are central to PD, and physical and psychological fatigue. In the following, the expected influence fatigue has on panic attacks, as the expected influence panic attacks have on the emergence of fatigue are displayed by dividing the mutual influence in subparts. (1) If a person experiences physical and psychological fatigue, daily challenges are perceived as being an excessive demand. (2) Due to the decrease in alertness and concentration, it becomes difficult to cope with those challenges (Jean-Louis, Von Gizycki, Zizi, & Nunes, 1998). (3) Furthermore, misinterpretation of daily demands and own abilities, trigger the thoughts and fears of experiencing a new panic attack due to overextension. A ‘radar system’ which detects potential panic arousing situations is steadily activated. Even simple daily decisions, like choosing an outfit or deciding on what to cook, are perceived as challenging and demanding. Thus, normal routines are suspended and a disconnection with other people and routines slowly takes place (Tubridy, 2008). (4) Aside from the constantly activated ‘radar system’,

which aims to detect and avoid panic evoking situations, a person's attention is highly selective for bodily sensations that could serve as an indicator for the next panic attack. According to Asmundson, Sandler, Wilson, and Walker (1992), this is due to the cognitive set of patients suffering from PD, which biases attention towards physical arousal. (5) The anxiety sensivity, leads to a misinterpretation of autonomic sensations (accelerated heart rate or sweating) that eventually raise a panic attack.

In addition to the influence fatigue has on the emergence of a panic attack, a panic attack can contribute to the emergence of fatigue. (6) Once a PD patient experiences his first panic attack, safety seeking behavior is commonly applied. This is crucial for the maintenance of PD (Salkovskis, Clark, Hackmann, Wells, & Gelder, 1999). Safety seeking behavior occurs as subtle stimulus avoidance and/ or escape behavior (Salkovskis, 1991).

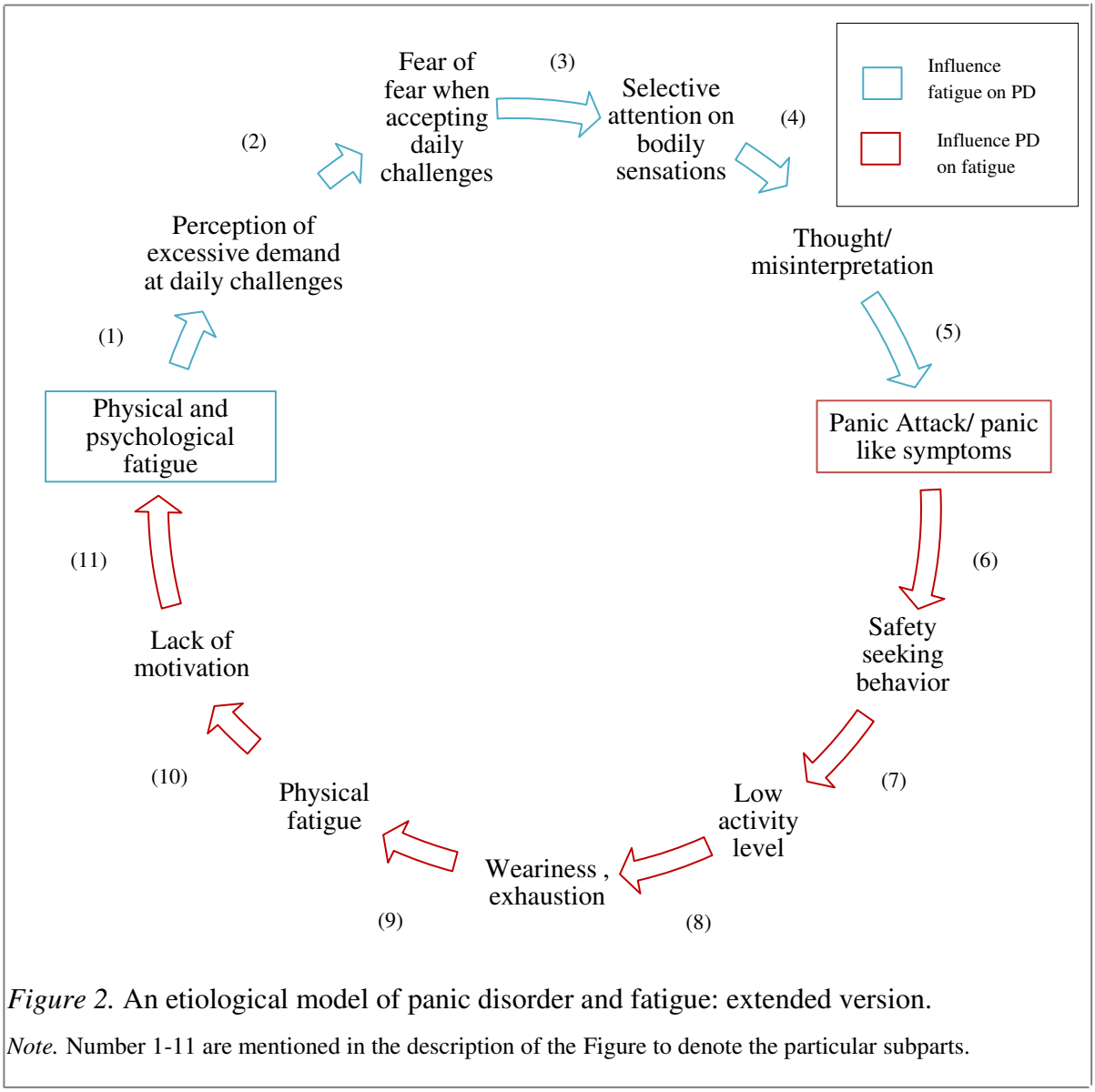

Figure 2. An etiological model of panic disorder and fatigue: extended version.

Note. Number 1-11 are mentioned in the description of the Figure to denote the particular subparts.

(7) Actually, as mentioned above, due to the 'radar system' PD patients consistently avoid potential panic evoking situations. In the long term, this causes a decrease in activity level. A low activity level has an effect on a potential social isolation of PD patients. Altogether, the impaired social functioning as well as a decrease in physical and emotional health leads to a significant impairment in a patient's quality of life in the long run (Markowitz, Weissman, & Ouellette, 1989). (8) According to Ensrud, Ewing, Fredman, Hochberg, Cauley et al. (2010), low physical activity and a person's state of weariness and exhaustion are associated with each other. Being physically inactive, not only enhances the risk to develop severe physical illnesses as cardiovascular diseases, but also affects a person's overall condition of physical health (Blair & Brodney, 1999). (9) This may lead to physical fatigue, which relies on bodily activity and energy loss (Shen, Barbera, & Shapiro, 2006). (10) The vicious circle is continued by the detrimental effect physical fatigue has on a person's motivation and his mental health (Lou, Kearns, Oken, Sexton, & Nutt, 2001), (11) which will finally contribute to the emergence of physical as well as psychological fatigue. According to Shen, Barber, and Shapiro (2006), suffering from both forms of fatigue induces symptoms of anxiety, which encloses the vicious circle of PD and fatigue. Altogether, the 'etiological model of panic disorder and fatigue' emphasizes again how close body and mind are related when thinking about the connection between PD and fatigue. This supports the need for a holistic approach when studying the relation between the etiology, maintenance, and treatment of both. Figure 3 displays a more compact version of the model described above.

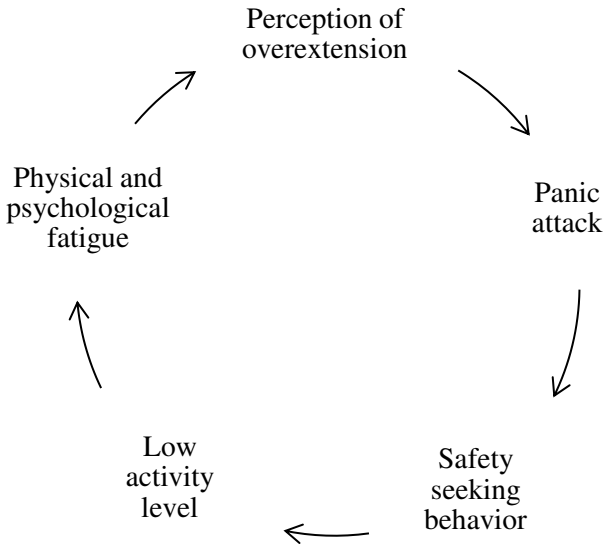

Figure 3. An etiological model of panic disorder and fatigue: abridged.

Research Questions

The aim of this systematic literature review is to point out existing knowledge concerning the relation between PD and fatigue. Therefore, the objective is to answer the following research question by collecting and assessing relevant and recent scientific literature: *To what extent is fatigue related to panic disorder?* To get a comprehensive answer to this question, the following three sub-questions are taken into closer consideration:

1. To what extent does fatigue influence the *etiology* of panic disorder?
   To what extent does panic disorder influence the *etiology* of fatigue?

2. To what extent does fatigue influence the *maintenance* of panic disorder?
   To what extent does panic disorder influence the *maintenance* of fatigue?

3. To what extent is fatigue treated within the common *treatment* concepts of panic disorder? (Psychological and Pharmacological)

Methods

In this systematic literature review comprehensive databases were screened on recent literature concerning the relation between PD and fatigue (and related phenomena). In order to give a review of relevant scientific studies and to guarantee evidence-based research, systematic review methods are used (Cuijpers, 2016). The aim of this study is to assess the relation between PD and fatigue by collecting and systematically analysing data on the etiology, maintenance, and treatment of PD with occurring fatigue.

Literature Search

An extensive literature search of exclusively scientific journal articles was conducted by the author in this review. To search, select, and collect relevant literature, the following electronic databases were used: Scopus, PsychInfo, Web of Science, ScienceDirect, and Google Scholar. The search was conducted in spring 2017 (March 2017- May 2017). To have a bigger variety and amount of relevant search results, the author decided to search for literature published in the last 30 years.

Search Terms

The key indexing term used by the author was *Panic Disorder*. To answer the research question, the search term *fatigue* was required in the search query. As mentioned above, the term *fatigue* is commonly associated with sleeplessness and related symptoms. Thus, it was decided to consider this multidimensionality when selecting appropriate search terms. Therefore, next to *fatigue,* the search terms: *sleepiness, tiredness*, *exhaustion,* and *lack of energy* were incorporated in the search. To answer the research question the Boolean operator 'AND' was used to combine the key-indexing term *panic disorder* with the search terms *fatigue/ sleepiness/ tiredness/ exhaustion/ lack of energy.* Furthermore, to answer the stated sub-questions, the search terms *etiology* (RQ 1)*, maintenance* (RQ 2), and *pharmacological treatment/ psychological treatment* (RQ 3) were added via the Boolean operator 'AND'. An overview of the search terms applied in this literature search is given in Table 1. An extended overview including used queries is displayed in Appendix A.

Table 1

Overview key Indexing Term and Search Terms in English

Key indexing term	Search terms	Query
Panic Disorder	Fatigue	'Panic Disorder' AND Fatigue*
Panic Disorder	Sleepiness	'Panic Disorder' AND Sleepiness*
Panic Disorder	Tiredness	'Panic Disorder' AND Tiredness*
Panic Disorder	Exhaustion	'Panic Disorder' AND Exhaustion*
Panic Disorder	Lack of energy	'Panic Disorder' AND 'Lack of energy'*

* The search terms 'Etiology', 'Maintenance', 'Pharmacological treatment', 'Psychological Treatment' were added to answer the sub-questions.

Literature Screening

Inclusion and Exclusion Criteria. Inclusion criteria when screening the literature were: literature concerning the etiology, maintenance, or treatment of PD, literature related to the etiology, maintenance, or treatment of fatigue/sleepiness/tiredness/exhaustion/lack of vitality, and literature related to fatigue/sleepiness/tiredness/exhaustion/lack of vitality in the etiology, maintenance, or treatment of PD. Furthermore, studies had to address participants that a) are diagnosed with PD as the main diagnose and b) that are not diagnosed with another main diagnose of mental or physical diseases. Exclusion criteria when screening the literature were: case reports, meta-analytic studies, literature reviews, book chapters; language other than English, German, and Dutch and literature about Chronic Fatigue Syndrome and fatigue caused by somatic diseases in relation to PD. Moreover, studies that did not approach fatigue and related symptoms were excluded.

Phases of Screening. As illustrated in Figure 4, the literature was screened in three phases of screening. In the identification phase (phase 1), First of all, the electronic databases were screened in detail regarding titles by using the above mentioned search terms and by applying the above mentioned in- and exclusion criteria. As a next step, duplicates were removed. In the screening phase (phase 2), the studies included after the first phase of screening were screened again in regard to their written abstracts by again applying the above mentioned in- and exclusion criteria. Studies of which no full abstract could be obtained were excluded from the data pool as well (Screening). In the third phase, the main texts of the selected literature were screened on full-text eligibility and contentwise by means of the in- and exclusion criteria (eligibility). Thus, a limited amount of literature, fulfilling the in- and

exclusion criteria, remained in the data pool after going through all three phases of screening. Furthermore, the references of the remaining literature were screened on relevant studies that were not identified before.

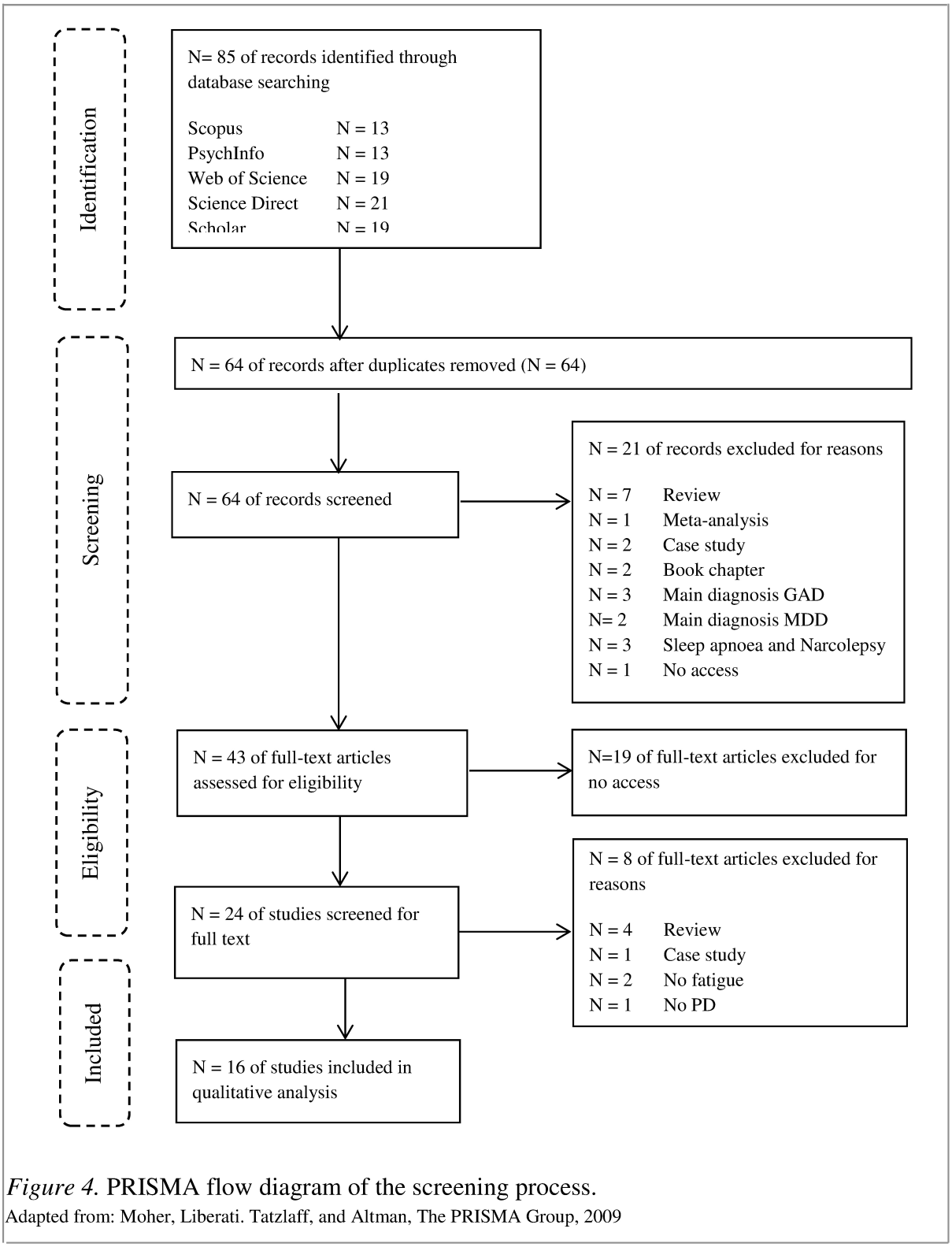

Figure 4. PRISMA flow diagram of the screening process.
Adapted from: Moher, Liberati. Tatzlaff, and Altman, The PRISMA Group, 2009

Data Extraction

After carefully reading the obtained literature, relevant data concerning the following issues was extracted: identification by name of the author(s), year of publication, location, article title, and journal name b) sample characteristics (study population) and sample size c) study outcomes and d) database. The extracted information from the obtained literature is summarized and displayed in Appendix B.

Results

Screening Results

For the first phase of screening in total N = 85 studies were selected based on its titles. The search terms displayed in Table 1, as the in- and exclusion criteria listed above were applied to identify the studies included in the first version of the data pool. Most articles were found concerning the relation between PD and fatigue in general (N = 54). In contrast, articles dealing with the research question concerning the psychological treatment (N = 4) of PD when considering fatigue represent the smallest amount of the research material. As displayed in Figure 4, which illustrates the selection process, N = 64 studies were included in screening phase 2. In this screening phase, N = 21 records were excluded from the data pool for several reasons (see Figure 4). Next, full-text eligibility is checked for the remaining articles (N = 43) in the data pool. After excluding N = 19 sources, N = 24 were included in the third screening phase. After performing this last screening, N = 8 studies were excluded from the final data pool. The in- and exclusion criteria that were responsible for the extraction of these studies have not been apparent in the first and second phase of screening. After performing the screening process described above, N = 16 studies were included in the final data pool and qualitative analysis. As mentioned in the exclusion criteria, it was planned to search for studies in English, German, and Dutch. During the search process it became apparent that just a small amount of studies has been published in German or Dutch, and that these studies do not match the in- and exclusion criteria. Thus, only studies written in English were selected and included in the final data pool. Appendix B displays studies that are included in the final data pool. An additional screening result that should be reported for future research is the finding that the search terms ‘lack of energy’ and ‘exhaustion’ as synonyms for fatigue did not yield any results in combination with PD.

Study Characteristics

An overview over characteristics of the studies included in the final data pool is given in Appendix B. It displays the authors’ names, the year of publication, the location of publication, the title of the study, the journal name, study population, the sample size and the database it was retrieved from. Most final studies were retrieved from ScienceDirect (N = 5), the fewest were retrieved from PsychInfo (N = 2). In addition, the query “Panic Disorder” AND fatigue caused most of the search results concerning the articles in the final data pool

(N = 10). Studies included in the qualitative analysis were published from 1984 to 2014, thus in a 30- year period. Furthermore it became apparent that most studies were published in the United States (N = 9) and in Europe (N = 5). Moreover, population size and characteristics are displayed in Appendix B. Sample sizes of study populations were mentioned in N = 15 studies. The range of sample size in the selected studies goes from 9 to 1168 participants. The mean age in all studies is 33.9. Two studies addressed children, while N = 16 studies addressed an adult population. Furthermore, a closer look was taken at the participants' symptoms and diseases. As displayed in Table 2, information concerning particular participant characteristics were given in N = 16 studies. In total only N = 3 studies in the final data pool focused on participants that experience PD and sleep problems.

Table 2

Disease Characteristics of Participants in N = 16 Studies in the Final Data Pool

	Patients with PD with or without agoraphobia	Patients with PD and/ or phobic disorders	Patients with anxiety disorder in general	Patients with PD and sleep problems
Number of studies	10	1	2	3

Etiology of Panic Disorder and Fatigue

As mentioned above, this systematic review aims to examine the relationship between PD and fatigue by focusing on the etiology of PD and fatigue among others. Thus, in order to answer the research questions: '*To what extent does fatigue influence the etiology of panic disorder?'* and '*To what extent does panic disorder influence the etiology of fatigue?'* the results of N = 6 studies, that yielded information regarding these research questions, are described in the following. As can be seen in the overview in Figure 5 and Table 3, various sleep characteristics, the sleep duration and the occurrence of nocturnal panic attacks account more or less for the etiology of PD and fatigue.

Sleep Characteristics. N = 3 studies that assessed sleep characteristics of PD patients found abnormalities in the Rapid Eye Movement (REM) sleep phase of patients that experience PD. This explains comorbid fatigue partly. Uhde, Roy- Byrne, Gillin, Mendelson, Boulenger, Vittone, and Post (1984) investigated the sleep of nine patients with panic and phobic disorders by means of EEG sleep recordings. All patients showed a shortened REM

latency and a decrease in total REM density. Furthermore, the movement time of PD patients was increased as compared to the controls. Additionally, it was found that high levels of arousal and psychomotor activity over day can be associated with higher activity levels at night. Similar results were found by Overbeek, Van Diest, Schruers, Kruizinga, and Griez (2005). The sleep complaints of 70 PD patients were examined. Five PD patients suffered from comorbid dysthymia and 31 patients reported to experience panic attacks at night. It was found that PD patients often suffer from an impaired arousal regulation, which is seen as an underlying mechanism to the pathology of PD. In addition, it was reported that PD patients had an increase in overall sleep complaints and a decrease in sleep efficiency in particular. Next to the abnormalities in sleep patterns that account for fatigue in adult PD patients, an Australian study assessed by Hudson, Gradisar, Gamble, Schniering, and Rebelo (2009) reports sleep patterns and problems in clinically anxious children from age 9 to 12. Surprisingly, compared to controls in the same age group no significant differences in sleep latency and number of awakenings during the night were found as.

Sleep Duration and Insomnia. Besides abnormalities during sleep, the duration and (in-) ability to fall asleep and/or sleep through the night serves as an explanation for fatigue in PD patients. N = 3 studies found deviation from the sleep time of controls. Firstly, Singareddy and Uhde (2009) assessed subjective sleep duration in four subgroups, namely (1) PD only, (2) PD with nocturnal sleep panic attacks, (3) PD with lifetime depression, (4) PD with nocturnal panic attacks and lifetime depression. The patients in subgroup (4) reported the greatest decrease in subjective sleep duration (5h or less). The greatest amount of sleep duration was reported by subgroup (3). Overall, 23% of PD patients suffered from severe sleep restriction or an increase in sleep duration. The role of insomnia in PD is also mentioned in a study conducted by Alvaro, Roberts, and Harris in 2014. To investigate the effects of depression and anxiety on insomnia data of 318 students was gathered. It was found that insomnia is predictive for PD, but not vice versa. The decrease in sleep duration is also confirmed by Uhde et al. (1984), who stated that PD patients sleep less than controls what may be due to their increased movement time during night.

Nocturnal Panic Attacks. Night time or nocturnal panic attacks (NPA's) awaken a concerned person from sleep. It evokes similar symptoms as a 'normal' panic attack over day. Overbeek, Van Diest, Schruers, Kruizinga, and Griez (2005) identify NPA's as the link between PD and sleep disturbances. In their study, seventy PD patients rated their subjective sleep characteristics. As a result, 77% of the PD patients that undergo NPA's report severe sleep complaints. 59% of the PD patients that do not suffer from NPA's have sleep

complaints too. In fact, it was found that the PD patients with NPA's have more problems in maintaining sleep than PD patients without NPA's. The second study that was concerned with the etiology of PD and fatigue, especially with NPA's, was conducted by Singareddy and Uhde in 2009. It was found that NPA's are associated with an increase in sleep disturbances. In particular, it was stated that poor sleep in PD patients contributes to the development of NPA's. Furthermore, NPA's were found to be a risk factor for the development of anxiety.

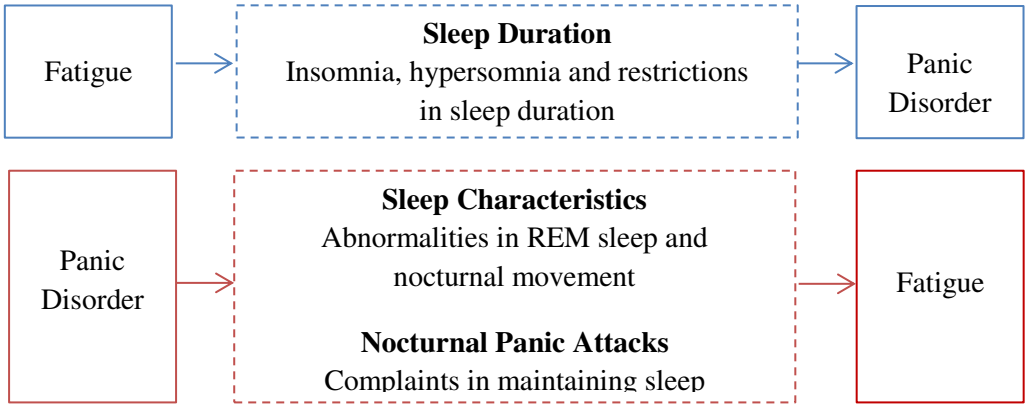

Figure 5. The mutual influence panic disorder and fatigue have on each other's etiology.

Summary. The literature review concerning the etiology of PD and fatigue revealed three aspects that account for the reciprocal influence PD and fatigue have on the etiology and development of each other. The relationship between both is illustrated in Figure 5. With regard to the research question '*To what extent does fatigue influence the etiology of panic disorder?'* it was found that most PD patients experience abnormalities in *sleep duration*. Besides sleep restriction even insomnia is common in PD patients.

The literature review revealed that PD has a greater influence on the etiology of fatigue than vice versa. The research question '*To what extent does panic disorder influence the etiology of fatigue?'* can be answered by presenting two findings. Firstly, various *divergent sleep characteristics* were found to be responsible for the development of fatigue in PD. Next to the decrease in REM latency, REM density and ability of arousal regulation, movement time and the extent of psychomotor activity are increased in PD patients. Secondly, *Nocturnal Panic Attacks* were found to account for the etiology of fatigue and related symptoms in PD patients, due to its detrimental consequences for the maintenance of sleep. As displayed in Figure 5, it was commonly found that N = 5 studies support the assumption that PD influences the etiology of fatigue in terms of abnormalities in sleep

pattern and NPA's. N = 1 study emphasizes the predictive role of Insomnia for the etiology of PD. It has to be considered that the studies report about sleep and related problems, but not explicitly fatigue.

Table 3.

Journal Articles Identified to Answer the Research Question on the Etiology of Panic Disorder and Fatigue

Author(s)	Title	Outcome
Alvaro, Roberts, & Harris (2014)	The independent relationships between insomnia, depression, subtypes of anxiety, and chronotype during adolescence	Insomnia was found to be predictive for PD.
Hudson, Gradisar, Gamble, Schniering, & Rebelo (2009)	The sleep patterns and problems of clinically anxious children	Children that experience PD have lower mean sleep time and different sleep patterns than controls in same age group. Sleep problems of children were found to predict the development of anxiety disorders in adults.
Overbeek, Van Diest, Schruers, Kruizinga, & Griez (2005)	Sleep complaints in PD patients	PD patients experience sleep complaints more often than healthy controls. Sleep efficiency and sleep duration are decreased. Further, impaired arousal regulation plays a role in the mechanism of PD. The potential link between PD and sleep complaints is seen in nocturnal panic attacks.
Singareddy & Uhde (2009)	Nocturnal sleep panic and depression: Relationship to subjective sleep in PD	Patients with PD or depression are at higher risk to have sleep problems or abnormalities in sleep duration (sleep restriction). Nocturnal panic attacks are associated with sleep disturbances in PD. Poor sleep in PD patients has consequences for the development of nocturnal sleep panic attacks.
Uhde, Roy-Byrne, Gillin, Mendelson, Boulenger, Vittone, & Post (1984)	The sleep of patients with PD: A preliminary report	PD patients were found to have shortened REM latency, less REM density, and higher total movement time than controls. PD patients with high levels of arousal and psychomotor activity over day have similar increased activity level at night.

Maintenance of Panic Disorder and Fatigue

The second aspect that was addressed in this review was concerned to the maintenance of PD and fatigue. Thus, the following research questions were formulated: '*To what extent does fatigue influence the maintenance of panic disorder?'* and *'To what extent does panic disorder influence the maintenance of fatigue?'* .To answer this questions, the findings of N = 3 studies were compiled and described in the following (see also Table 4).

Maladaptive Cognitive and Behavioral Processes. The review concerning the maintenance of PD and fatigue revealed that fatigue is persisting in PD patients due to several maladaptive cognitive and behavioral processes. These processes are examined by two studies. Firstly, Fairholme, Carl, Farchione, and Schonwetter (2012) conducted a study to assess the relationship between anxiety sensivity, dysfunctional beliefs, fatigue, safety behaviors, and insomnia in 59 outpatients with anxiety and mood disorders. It was found that anxiety sensivity is an underlying mechanism to the persistence of sleep disturbances in anxiety disorders. Furthermore it is revealed that dysfunctional beliefs (e.g. consequences of inadequate sleep), attentional biases (e.g. selective attention on signs of wakefulness or inadequate sleep), and conditioned safety behavior (e.g. active attempts to control own sleep) are key mechanisms in the persistence of insomnia. An example for an attentional bias might be coming home from work and still thinking about work related issues- this will be interpreted as a sign to be unable to fall asleep the coming night. Further, signs of fatigue over day are commonly interpreted as indicative signs of impaired functioning. Safety behavior results from the patient's dysfunctional beliefs and his/ her intention to compensate those concerns. An example for safety behavior might be a person who is convinced to not be able to cope with fewer than 7 hours of sleep. Thus, the concerned person may take naps over day. Those maladaptive processes were described in terms of a cycle (see Figure 6). The endorsement of anxiety increases the amount of dysfunctional beliefs related to insomnia. This in turn leads to cognitive biases and further the concerned person applies safety behaviors. As a result, the severity of insomnia increases and anxiety is endorsed. As a conclusion, it was found that the presence of anxiety increases the extent of maladaptive cognitive and behavioral processes and therefore the severity of insomnia. As a last finding from this study it was reported that the processes in insomnia overlap with the maladaptive processes in PD. Fairholme and Manber confirmed these findings in 2014. Moreover, this contemporary study focused on safety behavior of anxiety patients to a greater extent. N = 63 outpatients with a current anxiety or mood disorder were addressed. As a result, increased

sleep effort was added to dysfunctional beliefs and safety behavior as underlying mechanisms. Increased sleep effort was described as the active attempt to control own sleep. In the study it could be observed that concerned people reduce their daytime activity level on days that follow nights with poor sleep, for example. Nevertheless, it was emphasized that is not fully approved whether dysfunctional beliefs and increased effort are maintaining factors or if they are more a byproduct of anxiety.

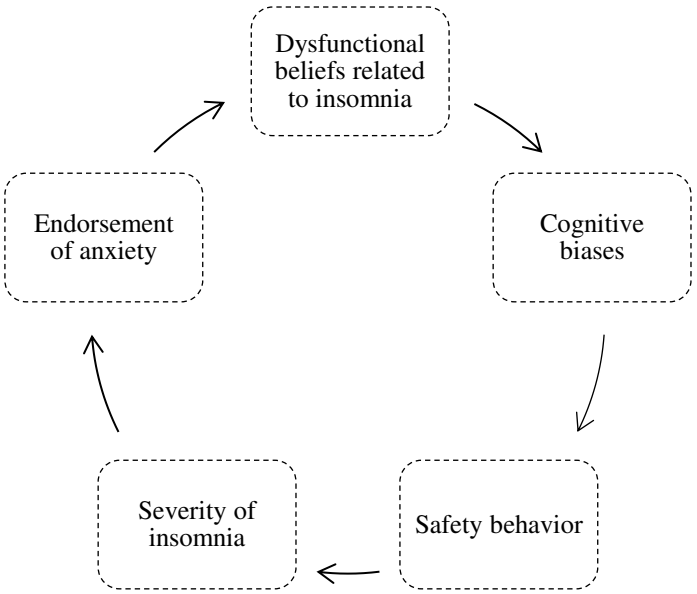

Figure 6. Maladaptive cycle of Panic Disorder on the maintenance of fatigue
based on findings of Fairholme, Carl, Farchione, & Schonwetter, 2012

Quality of Life. Next to studies that aim to explain the maintenance of PD and fatigue by means of maladaptive cognitive and behavioral processes, Simon, Otto, Korbly, Peters, Nicolaou and Pollack (2002) examined the quality of life in PD patients. In this study it was found that PD patients are impaired in physical functioning and mental health to a greater extent than social anxiety patients. It was stated that the decrease in physical activity affects a PD patient's vitality and energy level. Actually, this has detrimental consequences for the quality of life of concerned people.

Summary. To sum up the findings concerning the maintenance of PD and fatigue, it has to be emphasized that only the relation of PD on the maintenance of fatigue is reported, not vice versa. No literature was found regarding the research question '*To what extent does fatigue influence the maintenance of panic disorder?'* what means that the influence of fatigue on the etiology of PD is not examined, or that research findings are not published yet.

On the contrary, the research question *'To what extent does panic disorder influence the maintenance of fatigue?'* can be answered in terms of maladaptive cycles. Fairholme and colleagues (2012) conducted two studies and underlined the role of dysfunctional beliefs, cognitive biases, safety behavior and increased sleep effort in the persistence of insomnia and fatigue in PD patients. Furthermore, a study conducted by Simon and colleagues emphasized the impaired quality of life in PD patients that contributes to the persistence of fatigue and related symptoms.

Table 4

Journal Articles Identified to Answer the Research Question on the Maintenance of Panic Disorder and Fatigue

Author(s)	Title	Outcome
Fairholme, Carl, Farchione, & Schonwetter (2012)	Trans diagnostic processes in emotional disorders and insomnia: Results from a sample of adult outpatients with anxiety and mood disorders	Anxiety sensivity, dysfunctional beliefs, attentional biases and conditioned safety behaviour are underlying mechanisms for the maintenance of sleep disturbances in anxiety disorders.
Fairholme & Menber (2014)	Safety behaviors and sleep effort predict sleep disturbance and fatigue in an outpatient sample with anxiety and depressive disorders	Patients with PD that experience fatigue have dysfunctional beliefs about sleep, safety behaviour and increased sleep effort. This enhances the maintenance of insomnia. Moreover, these patterns are associated and contribute to with sleep disturbances in anxiety patients.
Simon, Otto, Korbly, Peters, Nicolaou, & Pollack (2002)	Quality of life in Social Anxiety Disorder compared with PD and the general population	Patients with PD experience great mental and physical impairments in quality of life.

Treatment of Panic Disorder and Fatigue

The last aspect that was assessed in this literature review to examine the relationship between PD and fatigue concerned the treatment of PD. For this, the research question '*To what extent is fatigue treated within the common treatment concepts of panic disorder? (Psychological and Pharmacological')* was formulated. In the following, findings on the pharmacotherapy of PD (N = 5), the possibilities of psychological therapy (N = 1), and combined treatment approaches (N =2) are described. An overview of the study results per treatment form is given in Table 5.

Pharmacological Treatment. In total N = 5 studies were identified that give insights in the pharmacological treatment of PD and/ or co-occurring fatigue and related symptoms. It got apparent that the studies report fatigue and related symptoms as sleep disturbances, drowsiness and insomnia as common adverse events of pharmacological treatment of PD patients. Those side effects are listed in nearly all medication classes to treat PD (see Table 5 for extended description of related study results).

Psychological Treatment. Next to pharmacotherapy, PD is commonly treated with psychological treatment forms. N = 1 study addressed fatigue in the psychological treatment of PD. Roy-Byrne, Craske and Stein (2006) emphasized the effectiveness of Cognitive Behavioral Therapy (CBT) for nocturnal panic attacks. It was found that false beliefs are apparent during sleep as well as over day what awakens concerned people and worsens their overall sleep parameters. Among others, CBT interventions address those false beliefs and catastrophic misinterpretations and are thus recommended to be applied for patients that experience NPA's.

Combined Treatment. The literature search has shown that a combination of two monotherapies aroused interest in recent years. Thus, it is decided to describe results concerning combined treatment forms (commonly pharmacotherapy and CBT) derived from N = 2 studies (see Table 5). Cervena, Matousek, Prasko, Brunovsky and Paskova (2005) explicitly addressed fatigue in the combined treatment of PD. Sleep disturbances of PD patients were assessed when being treated with psychotherapy (CBT), and with medication (Benzodiazepines and SSRI's). It was found, that the overall anxiety level of PD patients decreased after the treatment period. Further, the subjective sleep duration of PD patients increased, the sleep latency decreased and the sleep quality was improved to a small extent after treatment. As a conclusion, the study revealed that the sleep of PD patients shifted from stage one (superficial) to stage 4 (deep) sleep when treating with psychotherapy and medication. In addition, Marcus, Gorman, Shear, Lewin, Martinez, Ray, and Goetz (2007) conducted a study to compare side effects in PD patients being treated with pharmacotherapy only and being treated with pharmacotherapy and CBT. Thus, one group of patients with PD was treated with both, CBT and Imipramine and one group of PD patients was treated with Imipramine only. As a result, the patients treated with both treatment forms experienced less fatigue, weakness and sweating during the treatment than the other group of patients. Moreover, dropout was less in the group with PD patients that received both (3%) than in the medication only group (13%).

Summary. To answer the research question regarding the treatment of fatigue and PD: '*To what extent is fatigue treated within the common treatment concepts of panic disorder? (psychological and pharmacological'),* it has to be stated that no special attention is given to the improvement of fatigue when treating PD with pharmacotherapy. Rather, fatigue and related symptoms are listed as common side effects of PD medication.

With regard to psychological treatment concepts it was found that Nocturnal Panic Attacks could effectively be treated with CBT to improve sleep parameters. Finally, combined treatment has shown to be not only effective concerning an overall improvement of sleep quality, but to also reduce the side effect of fatigue and weakness that occur when PD patients are treated with medication only. When answering the research question formulated for the treatment of PD and fatigue it has to be concluded that fatigue is addressed to a small extent in psychological and combined treatment concepts only.

Table 5

Journal Articles Identified to Answer the Research Question on the Pharmacological and Psychological Treatment of Panic Disorder and Fatigue

	Authors(s)	Title	Outcome
Pharmacological treatment			
	Cassano, Toni, Petracca, Deltito, Benkert, Curtis, Hippius, Maier, Shera, & Klerman (2014)	Adverse- effects associated with the short-term treatment of PD with imipramine, alprazolam or placebo	Patients with PD who received treatment with Alprazolam had experienced adverse effects as fatigue, weakness and insomnia. Patients treated with Imipramine suffered from sleep disturbances and dizziness among others.
	Nardi, Valenca, Freire, Mochcovitch, Amrein, & Sardinhal (2011)	Psychopharmacotherapy of PD: 8- week randomized trial with clonazepam and paroxetine	The treatment of PD patients with paroxetine and clonazepam was compared. Clonazepam resulted in fewer amount of weekly panic attacks and decreased anxiety sensivity as compared to Paroxetine. Most common adverse effects were drowsiness and fatigue in both drugs.
	Seddon & Nutt (2007)	Pharmacological treatment of PD	About 75% of patients with PD have shown to benefit from pharmacological treatment. Due to its lower risk for dependence among others, antidepressants are preferred in the treatment of PD. Side effects of antidepressants are tiredness and sleep disturbances among others.

Table 5 continued

	Author(s)	Title	Outcome
Pharmacological treatment			
	Travis & Argvropoulos (2004)	Pharmacological treatment of PD	Adverse events of SSRI's are insomnia and headaches among others. Pharmacological treatment in PD patients has to be started with a lower dose than in depression.
	Uhlenruth, Starcevic, Qualls, Antal, Matuzas, Javaid, & Barnhill (2006)	Abrupt discontinuation of alprazolam and cognitive style in patients with PD-Early effects on mood, performance and vital signs	After abrupt discontinuation of pharmacological treatment with alprazolam, PD patients with higher baseline anxiety levels had more severe withdrawal symptoms. Further, patients treated with Alprazolam experience side effects as dizziness and sleepiness among others.
Psychological treatment			
	Roy-Byrne, Craske, & Stein (2006)	PD	Patients with PD can effectively be treated with Cognitive Behavioural Therapy. CBT can also be applied for nocturnal panic attacks.
Combined treatment			
	Cervena, Matousek, Prasko, Brunovsky, & Paskova (2005)	Sleep Disturbances in patients treated for PD	Patients with PD were effectively treated with CBT and pharmacotherapy. In addition, subjective sleep duration was longer, sleep latency was decreased and sleep quality was improved little, but significant.
	Marcus, Gorman, Shear, Lewin, Martinez, Ray, & Goetz (2007)	A comparison of medication side effects reports by PD patients with and without concomitant cognitive behaviour therapy	Patients with PD were treated with CBT and Imipramine experienced less fatigue, weakness and sweating than the patients that received Imipramine only. Moreover, dropout was less in the group with PD patients that received both (3%).

Discussion

The current review focused on the interrelation between panic disorder (PD) and fatigue. In particular, the reciprocal influence on their etiological processes, maintaining factors and the integration of fatigue in common treatment concepts for PD was examined. The aim of this systematic literature review was to give an extensive overview and description of characterizing aspects of the relation between PD and fatigue. In the following, main findings are outlined and discussed per research question in the light of the 'etiological model of panic disorder and fatigue' (see Figure 2) and other existing scientific studies on PD and fatigue.

'An Etiological Model of Panic Disorder and Fatigue' Revisited

To point out the first impression of research findings concerning the relation between PD and fatigue an 'etiological model of panic disorder and fatigue' (see Figure 2) was created in the introduction of this paper. After screening the literature and selecting relevant studies, the model is evaluated and extended based on the reviews main findings and additional scientific literature (see Figure 7).

The Blue, Upper Part Revisited. When answering all three research questions regarding the influence of fatigue on PD, it became apparent that the current literature revealed findings on the etiological influence only. *(1) Etiology.* In particular, the review identified a decrease in sleep duration and (in-) ability to fall asleep or sleep through the night to contribute to the etiology of PD. To give a more comprehensive suggestion for the etiological influence of fatigue on PD, the aspect of 'sleep duration' needs to be added to the blue, upper part of the 'etiological model of panic disorder and fatigue' (see Figure 7). The current literature did not confirm, neither reject the first impression of the literature illustrated in the upper part of the model due to a lack of research in this field. This assumes that the presumed influence fatigue has on the etiology of PD still needs to be further explored.

The red, Lower Part Revisited. In contrast, the review gave detailed insights into the influence PD has on the etiology and maintenance of fatigue, as well as into the influence PD treatment concepts may have for comorbid fatigue. When evaluating the lower, red cycle of the 'etiological model of panic disorder and fatigue' based on the reviews findings, the model needs be broadened to depict a comprehensive illustration of not only the etiological influence PD has on fatigue, but also on the maintenance and treatment.

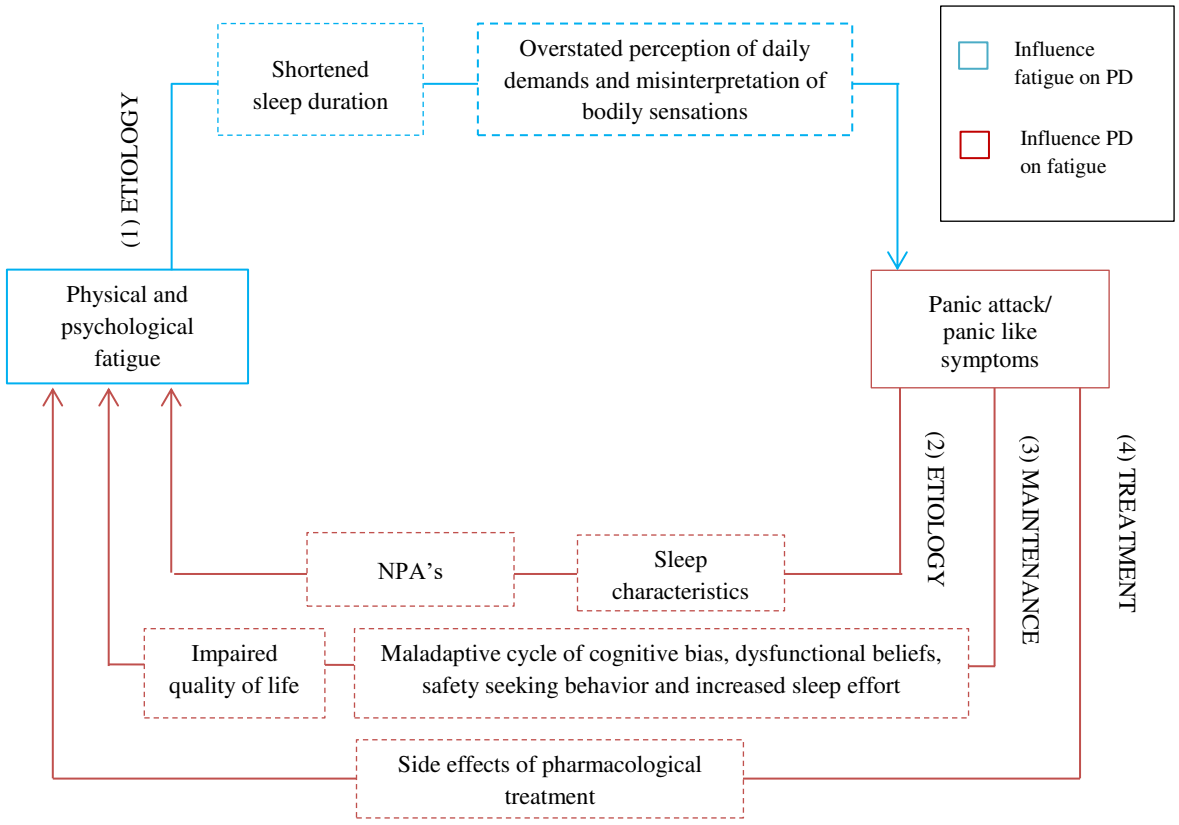

Figure 7. A holistic model of the relation between panic disorder and fatigue

Note. Number 1-4 are mentioned in the description of the Figure to denote the particular subparts.

(2) Etiology. The current review revealed that fatigue in PD patients is caused not only by divergent sleep characteristics, but also by worsened sleep parameters due to the occurrence of Nocturnal Panic Attacks (NPA's). These findings are consistent with other studies that consider the etiological relation between PD and fatigue. Hauri, Friedman, and Ravaris already stated in 1989, that the influence of PD and fatigue is characterized by a longer sleep latency, lower sleep efficiency, enhanced movement time and bodily activity, as well as by the occurrence of nightly panic attacks. Especially NPA's aroused the interest of researchers in the past years, due to the finding that 18-45% of PD patient experience NPA's (Papadimitriou & Linkowski, 2005). According to Singareddy and Uhde (2009), NPA's are likewise independently and interactively related to sleep disturbances in PD, and commonly seen as the link between PD and sleep complaints/ fatigue. Overall, the review emphasized the necessity to not overlook fatigue when diagnosing and understanding the emergence of PD. Therefore, 'sleep characteristics' and 'NPA's' are integrated in the model as explanatory factors for the etiological influence PD has on fatigue (see Figure 7).

(3) Maintenance. The current review declared two aspects that influence the maintenance of fatigue in PD patients- a maladaptive cycle of dysfunctional beliefs, cognitive biases, safety behavior and increased sleep effort, as well as an overall impairment in quality of life. Interestingly, additional scientific literature states that PD maintains fatigue due to their corresponding underlying mechanisms. Both, PD and fatigue are maintained by maladaptive cycles. When comparing both cycles it becomes apparent that they only differ with regard to the content of dysfunctional beliefs and the type of safety behavior or rather avoidance behavior. Dysfunctional beliefs in PD patients in general relate to the fear to undergo the next panic attack ('I will get a panic attack and lose control'). The dysfunctional beliefs in PD patients that experience fatigue and related symptoms refer to the fear of the detrimental consequences of insufficient sleep and rest on the concerned persons' daily life ('I can't function over day'). Furthermore, safety behavior in PD patients can be classified in three categories of behavior- direct avoidance, escape and subtle avoidance of potential panic evoking situations (Thwaites & Freeston, 2005). In contrast, safety behavior in insomnia is classified more in terms of its focus, which means whether it occurs in the daytime or at night (Ree & Harvey, 2004). Some patients that experience insomnia try to control the sleep itself; others reduce their daytime activity level on days that follow nights with poor sleep (Fairholme, Carl, Farchione, & Schonwetter, 2012) . Yet, safety behavior in both cycles shows patterns of reducing or avoiding potentially challenging situations. The high similarity in the underlying mechanisms of PD and fatigue in PD patients contributes to the maintenance of fatigue in PD.

The review again, neither fully confirmed, nor rejected the first impression of the literature (the etiological model of panic disorder and fatigue) regarding the maintenance of fatigue in PD patients. When comparing the main findings reported above with the first impression on the maintenance of fatigue in PD patients, illustrated in the lower part of the 'etiological model of panic disorder and fatigue', it gets apparent that the review's findings correspond with two aspects mentioned in the first impression of the literature. Firstly, the impaired quality of life of PD patients, with other words, the low activity level, lack of motivation and the state of exhaustion was found to account for the maintenance of fatigue. Secondly, the crucial role of conditioned safety behavior and increased sleep effort as key mechanisms to maintain fatigue in PD patients was confirmed. Additionally, the roles of cognitive bias and dysfunctional beliefs were identified in the review and should be taken into consideration when trying to explain the influence PD has on the maintenance of fatigue.

(4) Treatment. Besides the etiology and maintenance component of PD and fatigue,

the review gave insights into the integration of fatigue in the common treatment concepts of PD. Hereby it was found that fatigue is only addressed to a small extent. In particular, taking into account fatigue and the improvement of sleep parameters has been seen back in psychological and combined treatment concepts only. In contrast, fatigue and related symptoms were found to be listed as common side effects of pharmacotherapy to treat PD. These findings are also confirmed by current literature on the treatment of PD and fatigue. Barlow, Gorman, and Shear (2000) agree that a combination of Cognitive Behavioral Therapy and Psychopharmacotherapy is most effective (on the long run) when treating PD only. To ensure an effective treatment of comorbid fatigue, adaptions have to be made. Firstly, CBT should be extended with (graded) exercise therapy for example (Mock et al., 2005). Secondly, pharmacotherapy should not be used to treat PD patients with comorbid fatigue. The side effects of PD medication, as headache, fatigue or even insomnia, are seen as great disadvantage of this treatment form (Pande et al., 2000). Fatigue has to be seen not merely as a side effect of medication, but also as a possible maintaining factor for PD. Therefore, the side effects of PD medication have to be added when explaining the etiology and maintenance of fatigue in PD.

Conclusion on the 'Etiological Model of Panic Disorder and Fatigue'. The model based on the first impression of the literature formed a good basis for the explorative literature search. It was helpful to take into account different aspects that may be responsible for the relation between PD and fatigue. Indeed, the review's findings suggest that the 'etiological model of panic disorder and fatigue' needs to be extended with the issues discussed above to give a comprehensive overview of factors that account for the mutual etiology, maintenance, and integration of fatigue in the treatment of PD. When extending the 'etiological model of panic disorder and fatigue' with the issues of mutual maintenance and treatment, the new adjusted version of the model (see Figure 7) requires renaming the model in: 'A holistic model of the relation between panic disorder and fatigue'.

Limitations and Implications for Future Fundamental Research

Definition and Conceptualization of Fatigue and Sleepiness. First of all, the literature search revealed that especially the concepts of fatigue and sleepiness are used interchangeable by authors, therapists, and patients (Sangal, 2012). While some authors assessed the relation between PD and fatigue, others assessed the relation between PD and sleepiness. Indeed, it got apparent that most studies that aimed to focus on fatigue often

included the nature of sleep and the state of sleepiness to explain their results. This made it difficult to distinguish both concepts in the searching process. Furthermore, authors have their own conceptualization and understanding of both terms. The overlap and resulting lack of an accurate differentiation of fatigue and sleepiness in current scientific literature complicates to draw distinct and verifiable conclusions on research findings. For example, fatigue is often described as a side effect of psychopharmaca as Clonazepam (Benzodiazepine) and Paroxetine (SSRI). In case of Imipramine (TCA), sleepiness is listed as a common side effect. Further exploration of the conceptualization of fatigue and related concepts in general, as well as a clear differentiation and accurate definition of the concepts appears desirable and convenient for prospective fundamental research on fatigue.

The Problem of Comorbidity. Secondly, the literature search revealed several comorbidities of PD and fatigue with mental conditions like Generalized Anxiety Disorder (GAS) and Major Depressive Disorder (MDD) (Fischler et al., 1997; Breslau et al. 1992; Massion et al. 2002), as with physical diseases such as Fibromyalgia and Rheumatoid Arthritis (Hudson et al., 1992; Breslau et al., 1992; Katon et al., 1991). To ensure an accurate examination of the relationship between PD and fatigue, the applied exclusion criteria entailed an exclusion of studies that reported other main diagnoses than PD. Thus, studies that report not clinicopathologic symptoms of co-occurring medical and psychiatric conditions were included. Therefore, results of the current review may be biased by studies presenting a closer relationship between PD and fatigue than it is actually the case. In future fundamental research on the relation between PD and fatigue, an accurate examination of the relationship between PD and fatigue can only be ensured by fully excluding comorbid symptoms of other medical or psychiatric conditions.

During the screening process it became apparent that especially MDD and depressive symptoms affect the relation between PD and fatigue. According to Overbeek et al. (2005), comorbid depression explains the high prevalence of sleep complaints in PD patients. Depressive symptoms influence the relation between PD and fatigue in two ways. Firstly, research indicates depression to be a mediating factor in the relation between PD and fatigue (Alvaro, Roberts, & Harris, 2014). Secondly, comorbid depressive symptoms increase the severity and prevalence of sleep problems and, therefore, fatigue as well (Singareddy & Uhde, 2009). Reasoned by the linkage found between PD, fatigue, and depression, it is recommended to conduct further research on the relation between PD, fatigue, and depression.

Heterogeneity of the Included Sample. Thirdly, the studies included in the current review differed regarding their population samples. This could impair generalizability and the possibility to compare the study's findings. Firstly, the current review included participants from age 7 to age 74. The wide age range of the sample might be associated with the nature and severity of PD and fatigue. For example, the need to sleep varies with age to a great extent (Ohayon, Roberts, Zulley, Smirne, & Priest, 2000). Secondly, the sample sizes of the studies included in this review vary from 9 to 1168 participants, suggesting greater generalizability in contrast.

Recency of the Included Studies. The fourth limitation of the conducted review relates to the amount and recency of the included studies. While searching for relevant studies, the time span was extended to the year 1987 (past 30 years) due to the small amount of search results. This not only revealed the research gap in this field again, but also entailed disadvantages. Meanwhile, some studies are revised regarding treatment options and scientific findings (etiology and maintenance). Furthermore, study populations have changed. Especially the prevalence of PD and fatigue increased due to cultural and lifestyle changes as increased utilization of medical services (Walker, Katon, & Jamelka, 1993). As a conclusion, further exploration of the recent relation between PD and fatigue is needed.

Study Publication Bias and Selective Reporting Bias. The last limitation of the current review is that the results may have been impaired and distorted by study publication bias and outcome reporting bias (Dwan et al., 2008). Publication bias suggests that not all studies are actually published depending on the significance of the study's findings and that, thus, outcome data is missing (Cuijpers, 2016). Investigators, reviewers, and editors have the tendency to prefer the publication of positive or statistically significant results as compared to studies that found small effects of intervention or statistically not significant findings (Dickersin, 1990; Dwan et al., 2008). In consequence, this non-publication of negative studies leads to an overestimation of treatment effects, which threatens the reliable evidence of published literature. The current review is also likely to be biased by the study publication bias. Firstly, the bias in the included studies, which forms the basis for the results of this review, automatically leads to bias in the results of this review. Secondly, no qualitative research catalogue was used.

Besides, the current review might also be affected by within-study selective outcome reporting bias (ORB), which relates to published studies. It suggests that a particular subset of the original variables in a study is selected based on its results aiming to include it in a publication (Dwan et al., 2008). Thus, significant outcomes or outcomes with larger effect

sizes in a study are more likely to be fully reported while negative outcomes are missing or reported only partially (Cuijpers, 2016; Saini et al., 2014). As a consequence, Copas and Shi (2001) report that selective reporting bias leads to lower values of published studies and greater uncertainty regarding scientific literature.

Limitations and Implications for Clinical Practice

Diagnose of Comorbid Fatigue. In addition to the implications for future clinical research, this review may have some impact on the clinical practice as well. Overall, physicians and therapists are responsible for making an accurate diagnosis and for identifying possible comorbid symptoms and main diagnoses. In particular, physicians, and therapists are asked to be sensitive for fatigue and related symptoms in their PD patients. Especially when it comes to Psychopharmacotherapy, possible side effects of PD medication that could worsen fatigue and related symptoms need to be taken into consideration. Thus, a careful selection of PD medication has to be made by choosing the medication that implies the fewest side effects with regard to fatigue and related symptoms.

Integration of Fatigue in the Treatment of Panic Disorder. Moreover, the findings of this review suggest enhancing the integration of fatigue and sleep related psychological treatment concepts into the common treatment concepts of PD. Until today, CBT for PD only focuses on fatigue to a small degree. A huge number of researches have emphasized the effectiveness of CBT for PD. Bearing in mind the great similarity of the underlying mechanisms of PD and insomnia (see Figure 7), CBT may be effective to address insomnia, fatigue and related symptoms as well. To make suggestions for the integration of fatigue in CBT for PD patients, it is recommended to incorporate parts of the graded exercise therapy as has already been stated. Furthermore, psychoeducation on sleep hygiene could be beneficial for the improvement of fatigue and related symptoms due to its close relation with poor sleep (Alapin et al., 2000). Adjusting the common treatment concepts of PD patients to their needs concerning fatigue and sleep related problems, ‘[…] could avoid unnecessary and costly medical investigations and therapies.’ (Manu, Matthews, & Lan, 1988).

Conclusion

This systematic literature review gave a comprehensive overview of the relationship between PD and fatigue (and related symptoms) by investigating the mutual influence on etiological processes, maintaining factors, and the integration of fatigue in common treatment concepts of PD. The ‘etiological model of panic disorder and fatigue’, established on basis of the first impressions of the scientific literature served as a starting point for the explorative data search. The current findings indicated to expand and adjust the model, resulting in the ‘holistic model of the relation between panic disorder and fatigue’. This model can be seen as the first attempt to visualize the relation between PD and fatigue. Further, it can be seen as the starting basis for further exploration of the influence of PD and fatigue on the mutual etiology, maintenance, and treatment concepts. The ‘holistic model of panic disorder and fatigue’ should stimulate researchers and clinicians to consider comorbid fatigue and related complaints not only in the diagnostics, understanding, and treatment of PD, but also respectively other medical and psychiatric diseases.

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Appendix

Appendix A

Key Indexing Term, Search terms, Additional Search Terms and Search Query

Key indexing term	Search terms	Additional search terms	Search query
Panic Disorder	Fatigue		'Panic Disorder' AND Fatigue
Panic Disorder	Sleepiness		'Panic Disorder' AND Sleepiness
Panic Disorder	Tiredness		'Panic Disorder' AND Tiredness
Panic Disorder	Exhaustion		'Panic Disorder' AND Exhaustion
Panic Disorder	Lack of energy		'Panic Disorder' AND 'Lack of energy'
Panic Disorder	Etiology	Fatigue/ Sleepiness/ Tiredness/ Exhaustion/ Lack of energy	'Panic Disorder' AND Fatigue/ Sleepiness/ Tiredness/Exhaustion/ 'Lack of energy' AND Etiology
Panic Disorder	Maintenance	Fatigue/ Sleepiness/ Tiredness/ Exhaustion/ Lack of energy	'Panic Disorder' AND Fatigue/ Sleepiness/ Tiredness/ Exhaustion/ 'Lack of energy· AND Maintenance
Panic Disorder	Pharmacological treatment	Fatigue/ Sleepiness/ Tiredness/ Exhaustion/ Lack of energy	'Panic Disorder' AND Fatigue/ Sleepiness/ Tiredness/ Exhaustion/ 'Lack of energy' AND 'Pharmacological treatment'
Panic Disorder	Psychological treatment	Fatigue/ Sleepiness/ Tiredness/ Exhaustion/ Lack of energy	'Panic Disorder' AND Fatigue/ Sleepiness/ Tiredness/ Exhaustion/ 'Lack of energy' AND 'Psychological treatment'

Appendix B

Overview Studies Included in Final Data Pool with Additional Information

No	Author(s)	Year of publication	Location	Title	Journal	Study population	Sample size	Outcomes	Database
1	Alvaro, Roberts, & Harris	2014	Australia	The independent relationships between insomnia, depression, subtypes of anxiety and chronotype during adolescence	Sleep Medicine	High school students with sleep or mental health problems Age range 12-18	N = 318	Insomnia is predictive for PD.	PsychInfo
2	Cassano, Toni, Petracca, Deltito, Benkert, Curtis, Hippius, Maier, Shera, & Klerman	1994	Italy	Adverse- effects associated with the short-term treatment of PD with imipramine, alprazolam or placebo	European Neuropsychopharmacology	Patients with PD Age range 18-65	N = 1168	Treatment with Alprazolam and Imipramine has adverse effects as: fatigue, insomnia, weakness.	Web of Science
3	Cervena, Matousek, Prasko, Brunovsky, & Paskova	2005	Czech Republic	Sleep Disturbances in patients treated for PD	Sleep Medicine	Outpatients with PD Age range 19-50	N = 20	PD patients can effectively be treated with CBT and pharmacotherapy.	Scopus
4	Fairholme, Carl, Farchione, & Schonwetter	2012	United States	Trans diagnostic processes in emotional disorders and insomnia: Results from a sample of adult outpatients with anxiety and mood disorders	Behaviour Research and Therapy	Outpatients with anxiety and mood disorders Age range: 18-74	N = 59	Underlying mechanisms of sleep disturbances in anxiety. Anxiety sensivity, dysfunctional beliefs, attentional bias, conditioned safety behaviour.	Web of Science

Appendix B continued

No	Author(s)	Year of publication	Location	Title	Journal	Study population	Sample size	Outcomes	Database
5	Fairholme & Menber	2014	United States	Safety behaviors and sleep effort predict sleep disturbance and fatigue in an outpatient sample with anxiety and depressive disorders	Journal of Psychosomatic Research	Outpatients with a current anxiety or mood disorder Age range 18-74	N = 63	Dysfunctional beliefs, safety behaviour and increased sleep effort contribute to sleep disturbances in PD patients.	Science Direct
6	Hudson, Gradisar, Gamble, Schniering, & Rebelo	2009	Australia	The sleep patterns and problems of clinically anxious children	Behaviour Research and Therapy	Children with anxiety disorders Age range7-12	N = 37	Children with PD have lower sleep time than controls.	Science Direct
7	Marcus, Gorman, Shear, Lewin, Martinez, Ray, & Goetz	2007	United States	A comparison of medication side effects reports by PD patients with and without concomitant cognitive behaviour therapy	American Journal of Psychiatry	Patients with PD	N = 312	PD patients treated with Imipramine and CBT showed increase in overall sleep quality. Combined treatment showed less dropout rates.	PsychInfo
8	Nardi, Valenca, Freire, Mochcovitch, Amrein, & Sardinhal	2011	Brazil	Psychopharmacotherapy of PD: 8-week randomized trial with clonazepam and paroxetine	Brazilian Journal of Medical and Biological Research	Patients with PD and agoraphobia Mean age (group A) 35.9 (group B) 33.7	N = 120	Treatment with Paroxetine and Clonazepam results in adverse effects of fatigue and drowsiness.	Web of Science

Appendix B continued

No	Author(s)	Year of publication	Location	Title	Journal	Study population	Sample size	Outcomes	Database
9	Overbeek, Van Diest, Schruers, Kruizinga, & Griez	2005	Netherlands	Sleep complaints in PD patients	The Journal of Nervous and Mental Disease	Patients with PD	N =70	Sleep efficiency and sleep duration are decreased; arousal regulation is impaired in PD patients.	Google Scholar
10	Roy-Byrne, Craske, & Stein	2006	United States	Panic Disorder	General Psychiatry	-	-	CBT is effective for PD patients and to treat NPA's.	Google Scholar
11	Seddon & Nutt	2007	United Kingdom	Pharmacological treatment of PD	Psychiatry	Patients with PD	-	75% of PD patients benefit from pharmacological treatment.	Science Direct
12	Simon, Otto, Korbly, Peters, Nicolaou, & Pollack	2002	United States	Quality of Life in Social Anxiety Disorder compared with PD and the general population	Psychiatric Services	Patients with social anxiety disorder and Patients with PD	N = 66	Patients with PD experience great mental and physical impairments in quality of life.	Google Scholar
13	Singareddy & Uhde	2009	United States	Nocturnal sleep panic and depression: Relationship to subjective sleep in PD	Journal of Affective Disorders	Patients with PD and nocturnal sleep panic attacks, lifetime depression	N = 773	PD patients have enhanced risk to develop sleep problems. NPA's are associated with sleep disturbances.	Science Direct

Appendix B continued

No	Author(s)	Year of publication	Location	Title	Journal	Study population	Sample size	Outcomes	Database
14	Travis & Argyropoulos	2004	United Kingdom	Pharmacological treatment of PD	Psychiatry	-	-	75% of PD patients benefit from pharmacological treatment.	Science Direct
15	Uhde, Roy-Byrne, Gillin, Mendelson, Boulenger, Vittone, & Post	1984	United States	The sleep of patients with PD: A preliminary report	Psychiatry Research	Patients with panic and phobic disorders Age range 30-52	N = 9	PD patients have impaired sleep quality. Over day and nocturnal activity level are corresponding.	Scopus
16	Uhlenruth, Starcevic, Qualls, Antal, Matuzas, Javaid, & Barnhill	2006	United States	Abrupt discontinuation of alprazolam and cognitive style in patients with PD-Early effects on mood, performance and vital signs	Journal of Clinical Psychopharma cology	Patients PD with/without agoraphobia Age range 22-59	N = 26	Higher baseline anxiety levels predict more severe withdrawal symptoms after abrupt discontinuation.	Web of Science