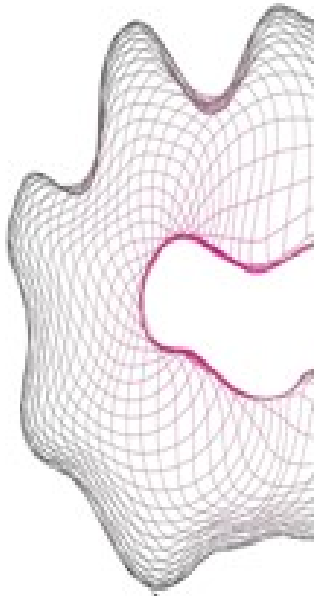


MASTERTHESIS

Fatigue and Generalized Anxiety Disorder (GAD): A Systematic Review of Etiology, Diagnosis and Treatment.



UNIVERSITY OF TWENTE.

Faculty of Behavioral Sciences

Study Program	Psychology
Master's specialization	Positive Psychology and Technology (PPT)
Author	Helena Jagow, s1188690
First attendant	Dr. Christina Bode Psychology, Health & Technology
Second attendant	Dr. Peter Meulenbeek Psychology, Health & Technology
Extent	10 EC
Date	15.10.2015

Abstract

Background and objective: Fatigue is a common human experience with diverse types and variations which often goes along with psychopathology. One of the most common psychopathological disorders that are related to fatigue is generalized anxiety disorder (GAD). Even though fatigue is commonly reported by GAD patients, the kind of relationship there is between fatigue and GAD, with regard to etiology, diagnosis and treatment, remains unclear. Therefore, the current review aims to answer the question to what extent and how fatigue is related to GAD with help of common systematic review strategies. **Method:** A systematic literature search was applied in the spring of 2015. A variety of search terms was used, including not only fatigue but also related concepts as tiredness, exhaustion, sleepiness, quality of sleep and vitality, due to the broad conceptualization of fatigue. Only published literature that yielded information on GAD, fatigue, etiology, diagnosis and treatment was included. **Results:** A total of 15 studies were included. Study characteristics were summarized and presented in tables; the included studies used different study designs, study populations and sample sizes. Eight theories on the etiology of GAD and fatigue were found, including an interrelationship between both, the Spielman 3P model, the metacognitive model of worry, the emotion dysregulation model of GAD and other explanatory models. The review yielded that fatigue is amongst the diagnostic criteria, but not essential in order to be diagnosed with GAD. The problem of comorbidity and overlapping symptoms was addressed. Different treatment options for GAD are known and described. The most common is CBT; other treatment options include exercise training or breaking the vicious circle of sleep and anxiety. Fatigue is not generally included in the treatment of GAD, even though there is indication that improving the one would lead to an improvement in the other. The problem of persistence of fatigue after successful treatment of anxiety is addressed. **Discussion and conclusion:** The current review concluded that the relationship between GAD and fatigue is not investigated entirely. It can be concluded that fatigue in GAD is caused by sleep difficulties provoked by excessive worrying, rumination and hyperarousal. The high comorbidity of GAD, especially with MDD, is indicating a great overlap of symptoms, amongst them fatigue, which could be traced back to a common underlying factor between both disorders. However, further research appears essential in order to make a distinction between fatigue that results from poor sleep or psychopathology.

Table of Contents

1.	Introduction	1
1.1	Relevance	1
1.2	Fatigue	1
1.2.1	Terminology	2
1.2.2	Measurement.....	3
1.2.3	Fatigue and Sleep.....	5
1.2.4	Fatigue and Anxiety.....	5
1.2.5	Treatment.....	5
1.3	Anxiety	6
1.3.1	Generalized Anxiety Disorder	7
1.3.2	Etiology.....	8
1.3.3	Diagnosis	9
1.3.4	Treatment.....	10
1.4	Research Questions	11
2.	Method.....	12
2.1	Literature Search.....	12
2.2	Search Terms	12
2.3	Literature Screening and Inclusion Criteria.....	13
2.4	Data extraction	14
3.	Results.....	14
3.1	Search Results and Study Characteristics.....	14
3.2	Etiology	20
3.2.1	Interrelationship between sleep and GAD	20
3.2.2	Spielman 3P model	20
3.2.3	Metacognitive model of worry	21
3.2.4	Emotion dysregulation model of GAD	22
3.2.5	Other explanations	22
3.3	Diagnosis.....	24
3.3.1	Fatigue.....	24
3.3.2	Problem of poor specificity and comorbidity	24
3.3.3	Sleep disturbance	25
3.4	Treatment.....	27

3.4.1 Cognitive behavioral therapy (CBT).....	27
3.4.2 Exercise training	28
3.4.3 Vicious circle of worry and sleep	28
4. Discussion.....	30
4.1 Summary of Evidence	30
4.2 Methodological Reflection and Theoretical Implications.....	37
4.2.1 Conceptualization of fatigue.....	37
4.2.2 Problem of comorbidity	38
4.2.3 Variety of studies	39
4.2.4 Bias	40
4.3 Conclusion for Future Research.....	41
4.4 Conclusion for Practice	42
5. Conclusion	42
Acknowledgment.....	43
References	43

1. Introduction

1.1 Relevance

It is long known that chronic physical diseases as rheumatism, pulmonary or cardiac diseases or cancer are often related to the experience of serious fatigue in patients. Serious fatigue has a great impact on the quality of life, the ability to fulfill daytime functions and even on the long – term life planning of patients with chronic diseases. Less is known about the relationship between psychiatric diseases, especially anxiety disorders and feelings of fatigue or exhaustion. Given the high prevalence and negative consequences of both, anxiety disorders and the experience of fatigue, further information appears eligible and necessary. There is a need to gather knowledge on the question which anxiety disorders are commonly related to fatigue, but also on the kind of relationship between those anxiety disorders and fatigue with regard to etiology and development but also the diagnosis and treatment options. The current study examines, with help of common systematic review methods, the relationship between Generalized Anxiety Disorder (GAD) and fatigue, and thereby aims to present conclusions on the literature that is available at the moment of searching, respecting knowledge on the development of fatigue and GAD, the inclusion of fatigue in the diagnostic criteria and the question whether fatigue is included in the treatment for GAD or not.

1.2 Fatigue

Amongst the most common human experiences is fatigue. Fatigue and related concepts as tiredness, sleepiness, exhaustion, lack of vitality or the consequences of poor sleep are commonly reported by both, the general population as well as medical and psychiatric patients. It is highly prevalent with prevalence rates ranging around 20% in the general population (Shen, Barbera & Shapiro, 2006). A problem concerning prevalence rates is addressed by a group of authors who describe that fatigue is likely to be under – reported by patients, resulting in impaired assessment of the prevalence of fatigue (Shen et al., 2006). Literature on fatigue implies that fatigue is related to a significant level of physical and psychosocial disorders (Bates, Schmitt, Buchwald, Ware, Lee, Thoyer, Kornish & Kamaroff, 1993; Shen et al., 2006; Sullivan, Kovalenko, York, Prescott & Kendler, 2003; Tsai & Lee – Chiong, 2013) as well as adverse health related outcomes such as mortality, morbidity and disability

(Meng, Hale & Friedberg, 2011; Shen et al., 2006). Literature on fatigue further suggests that fatigue is influenced by different variables as age, gender, physical condition, type of food, latency to last meal, mental status, personality type, life experience, health status and the psychopathological condition (Finsterer & Mahjoub, 2014). Furthermore, there is evidence that fatigue, as a result of sleep problems, often co – occurs with psychopathology, especially mood and anxiety disorders (Tkachenko, Olson, Weber, Preer, Gogel & Kilgore, 2014).

1.2.1 Terminology

Currently, there is no distinct generally accepted and used definition of fatigue, given that the concept fatigue is considered to be a complex phenomenon with diverse types and variations, which has led to the proposal of various definitions (Berrios, 1990; Finsterer & Mahjoub, 2014; Philips, 2015; Shen et al., 2006). The most popular consideration of fatigue is that it “describes a sensation related to exertion” (Philips, 2015) and appears under diverse circumstances (Finsterer & Mahjoub, 2014). From a medical point of view, fatigue is described as a condition resulting from previous stress or effort, which can lead to reversible impairment of performance and function, reduced motivation and activity but also to disturbances of the functional structure of the personality (Berrios, 1990; Smets, Garssen, Bonke & De Haes, 1995). Some authors differentiate this medical phenomenon of fatigue from the unexplained feeling of fatigue, which can be studied independently of physical phenomena, such as tiredness, and goes along with various medical and psychiatric conditions and diseases (Berrios, 1990).

As Shen et al. (2006) conclude there are various researchers who propose different approaches on defining fatigue. While some researchers define it in terms of the source, which could be the result of previous exertion, some others view it from a behavioral perspective, with fatigue being impairment in performance. Other groups of researchers distinguish normal fatigue from pathologic fatigue, or define normal fatigue as acute and pathological fatigue as chronic (Shen et al., 2006). Acute fatigue is therefore assumed to occur in healthy individuals as a protective function of the body with short duration in order to restore the body functions with rest (Shen et al., 2006). Chronic fatigue on the contrary affects clinical populations and is perceived as “abnormal, unusual, or excessive” with no distinct onset and a long duration (Shen et al., 2006). Chronic fatigue is not relieved by resting and affects the daily functioning

and quality of life of an individual (Shen et al., 2006). Finally, some authors claim to make a distinction between psychological and physical fatigue with psychological fatigue affecting motivation and being associated with stress and emotional experiences as anxiety and depression, and physical fatigue being defined as a loss of maximal capacity during activity which is associated with medical conditions as fever, infections or sleep disturbances (Shen et al., 2006).

However, there is still a broad lack of consensus about how fatigue can be generalized and how it can be distinguished from other overlapping concepts such as sleepiness, tiredness, stress, anxiety, burnout and boredom (Finsterer & Mahjoub, 2014; Philips, 2015; Shen et al., 2006). For example, even though sleepiness and fatigue are distinct phenomena, they are often used interchangeably, which impairs a precise recognition of fatigue explicitly (Shen et al., 2006). One explanation for this could be that they often coexist as a consequence of sleep deprivation and that patients themselves often group them together under the complaint of “being tired” (Shen et al., 2006).

Sleep disturbances or sleep problems are found to co – occur with and are a risk factor for psychopathological conditions but they also lead to the experience of fatigue or sleepiness (Tkachenko, Olson, Weber, Preer, Gogel & Kilgore, 2014). Therefore, it is difficult to differentiate between fatigue as a result of sleep problems or as a result of psychopathology. A broad overlap between these constructs impairs a good and valid diagnosis and leads to uncertainty about whether fatigue is a symptom of a medical or psychiatric condition or rather a disease itself, or whether it is the defining characteristic of a disease or one among others (Finsterer & Mahjoub, 2014; Tkachenko et al., 2014).

1.2.2 Measurement

In order to make eligible statements on fatigue, a valid diagnosis is necessary. Finsterer & Mahjoub (2014) suggest that fatigue may not only be a symptom, but rather a measurable dimension, which could therefore be classified and structured in measurement instruments. However, there are authors who claim that measurement of fatigue is highly subjective and that there is until today no objective tool to measure fatigue (Shen et al., 2006). Nevertheless this article is by now ten years old and there are various scales to measure fatigue. An overview about the eight most

common measurement instruments on fatigue, composed by Shen et al. in 2006, is presented in table one.

Table 1. *Common Measurement Instruments Fatigue*

<i>Name</i>	<i>Instrument</i>	<i>Dimensions</i>	<i>Aim</i>	<i>Psychometric properties</i>
BFI	9 – items	/	Screening and assessing clinical outcome in fatigued patients; identify severe fatigue	Good
CIS	20 – item self – report instrument	Subjective fatigue experience, concentration, motivation and physical activity level	Assess severity and phenomenology of fatigue; validated for CFS	Good
FAI	29 – items	Fatigue severity, situation specificity, consequences of fatigue, responsiveness to rest/sleep	Differentiate normal fatigue from medical disorders commonly associated with fatigue; distinguish differences between different diagnoses	Good
FIS	40 – items	Cognitive, physical and psychosocial functions; every – day life	Assess impact of fatigue on functioning areas	Good
FQ	14 items; 11 items in revision	Physical Fatigue and Mental Fatigue	Assessing fatigue in variety of medical disorders; used for patients with Chronic Fatigue Syndrome (CFS)	Good
FSS	9 – item	/	Measures of the impact of fatigue on specific types of functioning, behavioral consequences of fatigue rather than symptoms; to distinguish low fatigue from high fatigue	Good
MFI – 20	20 – item self – report instrument	General fatigue, physical fatigue, mental fatigue, reduced motivation, reduced activity	Severity of fatigue in the past week	Good
VAS – F	18 – items	Energy subscale, fatigue subscale	Assess behavioral manifestation of fatigue; measure subjective symptoms of fatigue	Good

- a. BFI: Brief Fatigue Inventory
- b. CIS: Checklist Individual Strength
- c. FAI: Fatigue Assessment Instrument
- d. FIS: Fatigue Impact Scale
- e. FQ: Fatigue Questionnaire
- f. FSS: Fatigue Severity Scale
- g. MFI – 20: Multidimensional Fatigue Inventory
- h. VAS – F: Visual Analogue Scale for Fatigue

1.2.3 Fatigue and Sleep

Literature on fatigue suggests that there is a close relationship between insomnia, or other sleep disorders, and fatigue or impaired functioning (Bélanger, Morin, Langlois & Ladouceur, 2004; Harvey, 2002; Herman, 2013; Shen et al., 2006; Tsai & Lee – Chiong, 2013). Poor sleep is therefore supposed to be a risk factor for fatigue and its consequences. Because fatigue often coexists with poor sleep and also is a consequence of sleep deprivation (Shen et al., 2006), there is a great number of studies on fatigue that include sleep related factors as well. Fatigue is thus often handled as a result of poor sleep. Another important factor in the literature on fatigue is that there is a great comorbidity of fatigue and psychopathology, especially with mood and anxiety disorders (Gillin, 1998; Tkachenko et al., 2006; Tsai & Lee – Chiong, 2013).

1.2.4 Fatigue and Anxiety

As mentioned above, fatigue often goes along with other psychopathological conditions. Literature suggests a correlation between fatigue and feelings of depression or anxiety, given that a significant number of patients that complain about fatigue also reveal such a condition (Bates et al., 1993; Berrios, 1990; Gillin, 1998; Tkachenko et al., 2006). More recent studies underline these findings by concretizing that fatigue correlates with psychological processes as major depression, generalized anxiety disorder and neuroticism (Shen et al., 2006; Sullivan et al., 2003; Tkachenko et al., 2006; Tsai & Lee – Chiong, 2013). Because correlation does not imply causation, it is still unclear of what kind this relationship is.

1.2.5 Treatment

Given the high comorbidity of fatigue with other psychopathology or medical conditions, there is not one generally accepted treatment for fatigue. It is assumed, that treatment of fatigue includes other factors as well, but further research on this topic appears essential in order to get a clear picture. There is, however, a generally accepted treatment for Chronic Fatigue Syndrome (CFS), a disorder characterized by serious fatigue persisting longer than six months and leading to considerable limitations in the everyday of the patients in question (Knoop & Bleijenberg, 2010). Furthermore there is a high congruence of CFS with pain and other somatic symptoms, even though CFS cannot be the primary diagnosis if fatigue can better be explained by another somatic or psychiatric disorder (Knoop & Bleijenberg, 2010).

Even though the presence of anxiety does not formally exclude the diagnosis CFS, there is reason to first treat the anxiety disorder, before concentrating on CFS, especially if it is about generalized anxiety disorder (GAD), given that excessive worry is assumed to co – exist with considerable fatigue (Knoop & Bleijenberg, 2010). Generally, the most accepted treatment options for CFS are graded exercise therapy (GET), which was developed in order to break the vicious circle of inactivity and declined physical condition, and cognitive behavioral therapy (CBT), which was developed to change the beliefs that maintain fatigue such a kind that limitations decline (Knoop & Bleijenberg, 2010). Based on the existing literature one can assume, that CBT is supposed to have a greater positive effect on fatigue related complaints. However, as the authors point out, what works for patients with CFS does not inevitably have to be effective for patients with other disorders that go along with fatigue, too (Knoop & Blijenberg, 2010).

1.3 Anxiety

Amongst the psychiatric disorders that are most commonly associated with fatigue are anxiety disorders. Anxiety is a term that includes a heterogeneous group of disorders with different epidemiology and symptomatology (Ebben & Spielman, 2008). Anxiety disorders are defined by either a specific and concrete fear or phobia of a specific object or situation, or an exaggerated, unspecific fear (Emmelkamp, Bouman & Visser, 2009). They are common, appear in different types and with different symptoms and go along with a range of somatic symptoms, as breaking out in sweat, shivering or sickness (Emmelkamp et al., 2009). Furthermore, anxiety disorders have a high comorbidity rate with, amongst others, depression. But while the relation between fatigue and depression either with or without comorbid anxiety is researched and reviewed multiple (Bennett, Ambrosini, Kudes, Metz & Rabinovich, 2005; Demyttenaere, De Fruyt & Stahl, 2005; Ferentinos, Kontaxakis, Havavi – Kontaxaki, Paplos & Soldatos, 2007; Ferentinos, Kontaxakis, Havaki – Kontaxaki, Paparrigopoulous & Dikeos, 2007; Mattisson, Bogren, Horstmann, Tambs, Munk – Jørgensen & Nettelblatt, 2009) this is not the case for anxiety disorders. Even though there seems to be a relation between anxiety and fatigue, given the fact that one of the most prevalent anxiety disorders, generalized anxiety disorder (GAD), includes fatigue as a criterion (Emmelkamp et al., 2009), there is still a broad lack of knowledge about the kind of relationship there is. It is therefore reasonable to either

assume an interrelationship between GAD and fatigue, or a vulnerability which would make it more likely to experience one, if you already suffer from the other. However, the question remains of which direction this vulnerability would or could be. Currently, literature about the relationship between anxiety and fatigue is not as explicit as one might expect based on the high prevalence of anxiety disorders and fatigue. This could be due to the fact that most studies on fatigue concentrate on comorbid sleep disorders or other somatic or psychiatric disorders, which impairs explicit statements on the relationship between anxiety and fatigue.

Another problem with existing literature about fatigue and anxiety is that this literature tends to be outdated. Given the fact that knowledge about anxiety disorders, and the diagnostic criteria especially, is changing rapidly, the focus should lie on current research. Finally, there is currently no systematic review on the relation between anxiety disorders and fatigue. However, there is a growing need to investigate this relation in order to form a distinct picture and improve diagnosis and treatment of anxiety with fatigue.

1.3.1 Generalized Anxiety Disorder

The only noted anxiety disorder that includes fatigue in the diagnostic criteria is generalized anxiety disorder (GAD) which is therefore further investigated in the current review on fatigue and anxiety. The cardinal symptom of GAD is an enormous and constant amount of rumination and worry over different life domains and topics (Emmelkamp et al., 2009). This excessive rumination concentrates on worst case scenario's which could happen in the future, as the development of serious diseases of oneself or beloved family members, unemployment, finances, loss of control or being in an accident. Patients with GAD have no control of these thoughts, which often result in fear (Emmelkamp et al., 2009; Vandereycken, Hoogduin & Emmelkamp, 2008). In addition to excessive rumination, patients with GAD report at least one of the following complaints: restlessness, concentration problems, irritability, muscle tension complaints, sleeping problems and fatigue (Vandereycken et al., 2008; Emmelkamp et al., 2009). GAD goes along with increased arousal and severe limitations to everyday life, and untreated the typical cause is chronic (Emmelkamp et al., 2009; Fricchione, 2004; Vandereycken et al., 2008). The diagnosis GAD is given when these complaints last longer than six months and are present on most days during this period (Emmelkamp et al., 2009; Fricchione, 2004;

Vandereycken et al., 2008). The problem concerning diagnosis is that GAD has a high comorbidity rate with amongst others depression and sleeping disorders. About half of the patients with GAD also report depressive symptoms (Emmelkamp et al., 2009). Given this information, there is evidence that there is a relation between GAD and fatigue. Unclear is, however, of what kind this relation is. This is because there is evidence that insomnia, which is strongly related to fatigue, can be a symptom of psychopathology, but also an important risk factor for, amongst others, major depressive disorder (MDD) (Morin, Bélanger & Fortier – Brochu, 2006). Due to some shared symptoms of MDD and GAD, amongst them fatigue, one might therefore assume that insomnia could also be a risk factor for GAD as well.

1.3.2 Etiology

There are different theories with regard to the etiology of GAD. The most common are summarized in Emmelkamp et al. (2009) who provided a general picture of this disorder in comparison to other anxiety disorders. Various factors can be important in the development of GAD including disturbed information processing of threatening information or missing confidence in the own problem solving strategies (Emmelkamp et al., 2009). The authors furthermore explain the important role of rumination and refer to a theory which claims that GAD patients worry in order to prevent themselves from undergoing negative experiences and pictures, given that worrying is a “pure verbal – linguistical process” and thus more abstract than imagination (Emmelkamp et al., 2009, p. 58). This blocking of emotional processing impairs effective problem solving aimed at processing correcting information, which leads patients to experience negative consequences in the long term (Emmelkamp et al., 2009). Meanwhile this theory is empirically supported with the conclusion that GAD patients are characterized by deficient emotion regulation in general, leading to inadequate emotion regulation strategies (Mennin, Heimberg, Turk, & Fresco, 2005). Other theories about GAD include cognitive and interpersonal theories. The authors refer to the theory of Wells who concluded in 1995 that positive and negative metacognitive processes are important in onset and maintenance of GAD. In 2009 there still was little empirical support for this theory (Emmelkamp et al., 2009). Various authors also highlighted the role of interpersonal problems, indicated by research that showed that GAD patients worry about relationship problems, report more interpersonal problems and are often characterized by an insecure attachment

(Emmelkamp et al., 2009). Finally there is little research on psychobiological processes of GAD. There is, as is summarized by Emmelkamp et al. (2009) small evidence that the psychophysical reaction pattern of GAD patients is characterized by decreased variability and flexibility, which is by the authors interpreted as evidence for a general dysregulation of arousal and inhibition systems (Emmelkamp et al., 2009). Heredity is estimated to contribute to the development of GAD for about 30% (Emmelkamp et al., 2009).

The authors also mention the problem of comorbidity in research on etiology of GAD. Especially depressive disorders are comorbid in about 50% of all GAD patients. Many of the problems described by GAD patients can possibly be ascribed to these comorbid depressive complaints (Emmelkamp et al., 2009), amongst them fatigue and sleep difficulties. Moreover there is evidence that GAD patients with comorbid depression also score higher on some typical GAD characteristics, indicating the comorbid depression to negatively impact the course of the anxiety disorder (Emmelkamp et al., 2009).

1.3.3 Diagnosis

As mentioned above, there is a broad overlap between symptoms of GAD and symptoms of depressive disorders. Also, there is a high rate of comorbidity between GAD and MDD. These shared symptoms, amongst them fatigue, and the high comorbidity rate impair a good and distinct diagnosis of GAD. However, there is not one instrument to diagnose GAD, but rather a combination of structured interviews and an accurate anamnesis and diagnostic skills of trained professionals. An overview of the most common diagnostic instruments on GAD, composed by Emmelkamp et al. (2009), is presented in table two.

Table 2. *Common Measurement Instruments GAD*

<i>Name</i>	<i>Instrument</i>	<i>Dimensions</i>	<i>Aim</i>	<i>Psychometric properties</i>
MCQ	65 – items self – report instrument	5 subscales: positive opinion about worry, opinions about checkability, metacognitive efficacy, negative opinions about worry and cognitive self – awareness	Measure metacognition on worry and rumination; assessing the way patients estimate or rank worry	Satisfying
M.I.N.I.	Structured interview	Divided into modules identified by letters corresponding to categories	Psychiatric structured diagnostic interview in order to briefly assess DSM – IV and ICD – 10 psychiatric disorders	Good
PSWQ	16 – items self – report instrument	/	Ranking statements on how relevant they are for handling worry and rumination	Good
SCID - IV	Semi – structured interview	Diagnostic modules, including all DSM disorders	Psychiatric semi – structured diagnostic interview to assess DSM disorders	Good
WDQ	25 – items self – report instrument	/	Subjects over what respondents could worry	Favorable

- a. MCQ: Meta Cognitions Questionnaire
- b. M.I.N.I.: Mini International Neuropsychiatric Interview
- c. PSWQ: Penn State Worry Questionnaire
- d. SCID – IV: Structured Clinical Interview for DSM – Disorders
- e. WDQ: Worry Domain Questionnaire

1.3.4 Treatment

GAD is generally treated with either a form of cognitive – behavioral therapy (CBT) or psychopharmacology. While CBT for GAD is validated, well studied and shown to be the most effective (Bélanger et al., 2004; Belleville et al., 2004; Ebben & Spielman, 2008; Emmelkamp et al., 2009), there is still uncertainty about the preference of psychopharmacological treatment. Literature suggests that either selective serotonin reuptake inhibitors (SSRIs) or benzodiazepines are the most effective forms of pharmacological treatment of GAD (Emmelkamp et al., 2009). But given the high likelihood of addiction and side effects, SSRI's are preferable to benzodiazepines (Emmelkamp et al., 2009). However, there are negative side effects that are common

in users of SSRI's, too, amongst them sleep disturbances (Ferguson, 2001). In the context of the current review, which examines the relationship between GAD and fatigue, which is supposed to be likely to be caused by sleep difficulties, it appears necessary to exclude psychopharmacological treatment options in order to prevent the results from being deformed. Another argument for the choice of cognitive therapies over psychopharmacology is given by the fact that there is a high comorbidity of GAD with addiction of alcohol or anxiolytics (Emmelkamp et al., 2009). Given this high comorbidity, one might want to forbear from giving GAD patients pharmacology that is also assumed to have a high risk for addiction, as it is in benzodiazepines. Hence, the current review concentrates on treatment of GAD that is based on cognitive theories, as the most commonly used, CBT.

The good efficacy of CBT can be explained with the main criterion of GAD, which is a form of worry or rumination. Those cognitive processes are supposed to be sensitive to cognitive approaches. CBT for GAD is built up of different elements. Patients are taught to register anxiety – triggers and be aware and sensitive to signals that trigger worry and rumination but CBT also includes cognitive restructuring, learning new coping skills or imaginary exposure (Emmelkamp et al., 2009). Interestingly, the preferred treatment option for both, GAD as well as CFS is a form of CBT, suggesting that the cognitive component could be an underlying factor.

Apart from CBT and psychopharmacology, there are other effective therapies for treating GAD. Those include relaxation or exercise therapies, metacognitive therapy, mindfulness and acceptance and commitment therapy or an integration or combination of different therapy approaches (Emmelkamp et al., 2009; Herring, Jacob, Sveveg & O'Connor, 2011). In the current review it could therefore be interesting to further investigate which treatment is used in the context of fatigue in GAD patients, and to take a closer look at the question to what extent the treatment of fatigue is integrated in the treatment of GAD, with regard to effectiveness.

1.4 Research Questions

Accordingly, the purpose of this study is to answer the following research question: Of what kind is the relationship between GAD and fatigue? In order to answer this question, the following sub questions are to be analyzed: 1) To what extent is fatigue related to the etiology of GAD? 2) Which role does fatigue play in the diagnosis of

GAD? 3) How is treatment of fatigue included in the common treatment of GAD? By means of this systematic research the scientific findings on this topic shall be collected, sorted and weighted. Based on these results a conclusion shall be carefully worded.

2. Method

Comprehensive and current databases were used to catalog fatigue and GAD. The evidence database for the catalog was assembled using established systematic review methods. Main objectives of this study were to analyze the relationship between GAD and fatigue and to summarize the effect this relationship has on etiology and diagnosis of GAD as well as to summarize the extent to which the treatment of fatigue is included in the treatment of GAD.

2.1 Literature Search

A broad search of the published English – language literature was performed by the author, using the common electronic databases Scopus, Science Direct and Psyc Info. The search was performed in the spring of 2015. It was limited to English – language studies, articles, systematic reviews and book chapters, published between 2000 and 2015.

2.2 Search Terms

Given the fact that until now the term fatigue is not as distinct as one would assume, the search terms also included synonyms that are commonly used by patients and researchers. Furthermore, the search was performed including search terms that address poor sleep and sleep related problems, based on the close relationship between poor sleep and fatigue in psychopathology. Therefore, the key indexing term generalized anxiety disorder was used, combined with the search terms fatigue, tiredness, exhaustion, vitality, lack of energy, quality of sleep and sleepiness, as well as diagnosis, treatment and etiology. These search terms were combined using the operator “AND”. An overview of the used key indexing term and the search terms and combinations for the research question is illustrated in table three.

Table 3. Overview key indexing term and search terms for research question

<i>Key indexing term</i>	<i>Search terms</i>	<i>Combination research question (AND)</i>
Generalized anxiety disorder	Fatigue	Generalized anxiety disorder AND fatigue*
Generalized anxiety disorder	Tiredness	Generalized anxiety disorder AND tiredness*
Generalized anxiety disorder	Exhaustion	Generalized anxiety disorder AND exhaustion*
Generalized anxiety disorder	Vitality	Generalized anxiety disorder AND vitality*
Generalized anxiety disorder	Lack of energy	Generalized anxiety disorder AND lack of energy*
Generalized anxiety disorder	Quality of sleep	Generalized anxiety disorder AND quality of sleep*
Generalized anxiety disorder	Sleepiness	Generalized anxiety disorder AND sleepiness*

* Additional search terms per sub question: etiology or diagnosis or treatment

2.3 Literature Screening and Inclusion Criteria

Study selection was accomplished through two levels of study screening. At level one screening, abstracts were reviewed for the following exclusion criteria: case reports, date of publication not within 2000 and 2015, languages other than English, studies about somatic disorders in combination with fatigue and/or GAD, studies that only measure the effect of psychopharmacology and studies about CFS patients. Full articles were then obtained for all studies accepted at level one. For level two screening, inclusion required that the studies dealt with information about GAD and at least one of the following categories of information: etiology, diagnosis or treatment of GAD, information about etiology, diagnosis or treatment of fatigue, information about the relation between GAD and fatigue, information about sleep disorders and the consequences. Study populations and samples were required to include participants that a) are diagnosed with GAD and b) report symptoms of fatigue, tiredness, sleepiness, exhaustion, lack of energy, lack of vitality or poor sleep.

2.4 Data extraction

Each study was then carefully read and the relevant data was extracted. Extracted data included the following information by each study: a) identification by name of the authors, publication date, location, source of article as book title or journal and the digital object identifier (DOI) number b) description of the study, study design and intervention details c) sample characteristics as study population and sample size and d) main results. The extracted data was summarized by sub question in tables six to eight.

3. Results

3.1 Search Results and Study Characteristics

Using the search terms and combinations listed above, a sum of 15 studies was found to be included in the current study. A flowchart was designed to document the process of deciding and choosing articles that were used for this systematic review on the basis of the given inclusion and exclusion criteria. This flowchart is illustrated in figure one. Of those 15 articles that were included in the final sample, two studies were Randomized Controlled Trials (RCTs), two were book chapters and one was a journal article, three studies used a cross – sectional design, two studies a longitudinal design and two studies retrospective designs. The other three studies were other forms of articles. The selected studies came from three different continents including two studies from Europe, twelve articles from North America and one article from Asia. Various study populations were used, including GAD patients only, GAD patients with comorbid psychopathology, patients with anxiety disorders, amongst which GAD, or a random sample of individuals. One study assessed children and adolescents, one study concentrated on elderly patients with 65 years of age and older; the other studies included adult patients between 18 and 65. Characteristics of the included articles are presented in table four, sorted by the name of the corresponding author.

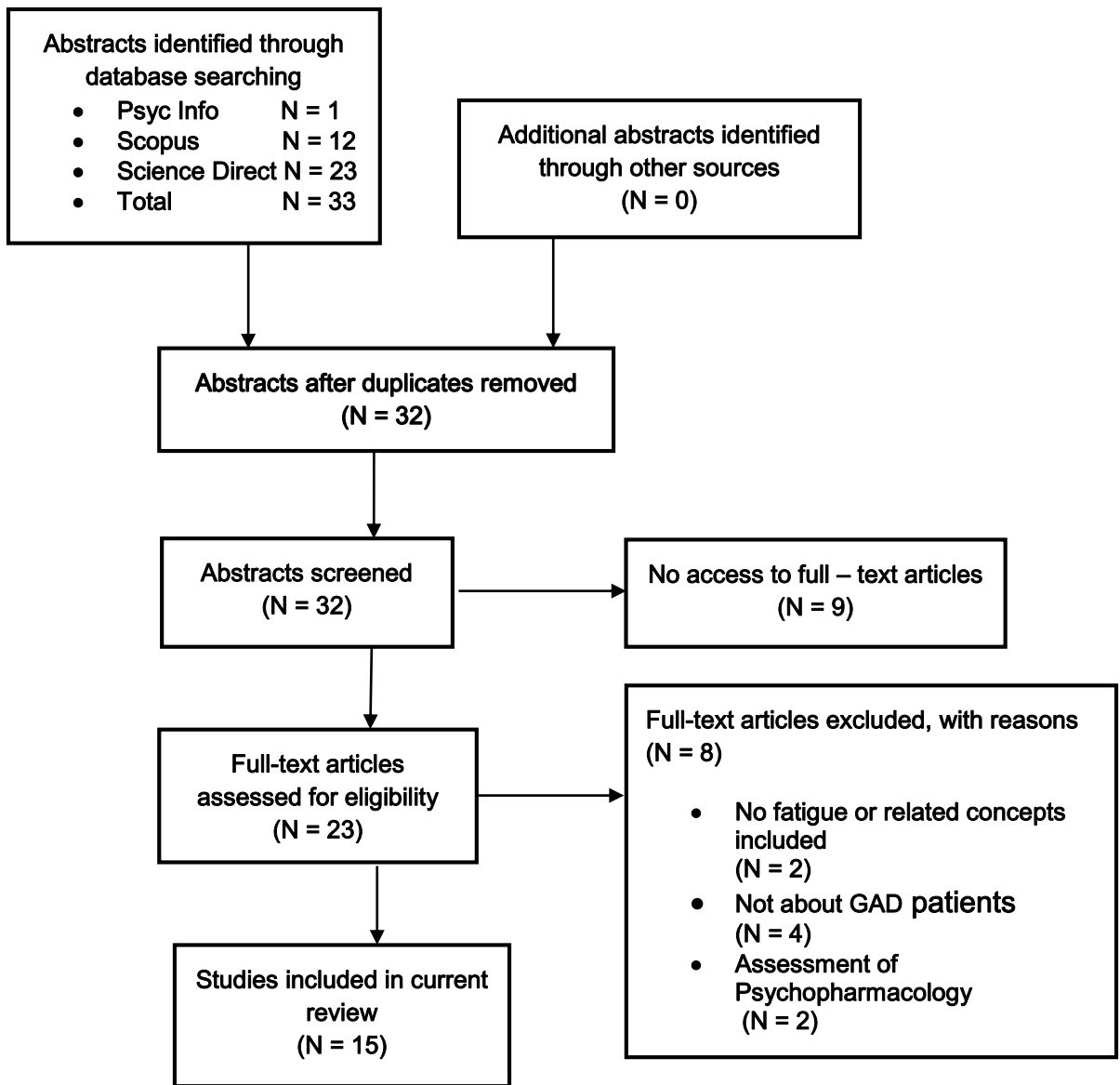


Figure 1. Flowchart of the searching process

Table 4. *Study Characteristics*

<i>Authors</i>	<i>Year</i>	<i>Location</i>	<i>Objective</i>	<i>Study Population</i>	<i>Sample Size</i>	<i>Study Design</i>
Bélanger, Morin, Langlois & Ladouceur	2004	Québec	Examination of the impact of treating GAD with CBT interventions on insomnia symptoms	French – speaking Caucasians with a primary GAD diagnosis	N = 44	Analytic: RCT with experimental group that received CBT treatment specifically targeting worry in GAD and waitlist control group
Ebben & Spielman	2008	New York	Discussion of the relationship between a select group of anxiety disorders (GAD) and sleep disturbance	/	/	Book chapter
Fairholme & Manber	2014	Boston	Theoretical and empirical support for the role of insomnia specific cognitive – behavioral dysfunctional beliefs, safety behaviors and increased sleep effort in the maintenance of insomnia and fatigue in the context of anxiety and mood disorders	Outpatients of the Boston Center for Anxiety and Related Disorders, diagnosed with a current DSM – IV disorder	N = 63 25% GAD patients	Descriptive: Cross – sectional design of self – report measures of various questionnaires prior to treatment; multivariate path analyses of disorder and results
Faravelli, Castellini, Benni, Brugnera, Landi, Lo Sauro, Pietrini, Rotella & Ricca	2012	Florence	Evaluation of the coherence of GAD psychopathological pattern, the robustness of the diagnostic criteria and the clinical utility of considering this disorder as a discrete condition rather than assigning it a dimensional value	Community sample; data from the Sesto Fiorentino Study; subjects diagnosed with GAD	N = 105 17.1% no comorb., most freq. comorb. MDD, 70.4%	Analytic: Reanalysis of data from the Sesto Fiorentino Study; Bottom – up design in which symptoms were assessed by clinical psychiatrists according with a nosographic system of reference
Herring, Jacob, Suveg & O'Connor	2011	Athens	Effects of short – term exercise training on signs and symptoms of generalized anxiety disorder	Sedentary women, 18 – 37, diagnosed with GAD and not engaged in treatment other than pharmacotherapy	N = 30	Analytic: RCT with two experimental groups - six weeks of RET, AET or wait list (WL); RET: 2 weekly sessions of lower – body weightlifting, AET: 2 weekly sessions of leg cycling matched with RET
Lijun, Ke – qing, Xiuli, Ze, Qinpu, Yanchao, Lianghai, Yang, Jianfeng, Yongqiao, Laohu & Hua	2012	Baoding	Investigation of sleep characteristics of a community sample of patients with 13 types of mental disorders	Subjects >18 years sampled from the Epidemiologic Sites Survey of Mental Illness at a mental health center in Hebei Province, China; participants met the diagnostic criteria of 13 types of mental disorders according to DSM – IV – TR Axis 1	N = 1874 exp., N = 15117 control N = 127 ind. with GAD	Analytic: Retrospective cohort study; descriptive: cross – sectional study; statistical analyses of the association of sleep quality and GAD in comparison to other DSM – IV – TR diagnoses
Marcks, Weisberg, Orlando Edelen	2010	Providence	Examination of the relationship between sleep disturbance and the course of anxiety disorders in primary	Participants part of the Primary Care Anxiety Project (PCAP); only participants with	N = 533	Naturalistic, longitudinal study of anxiety disorders in primary care; intake evaluation, follow – up after 6, 12, 24, 36, 48 and 60 months

& Keller			care patients	sleep data at intake; > 18 years; participants with one or more anxiety disorder (GAD)			
Morin, Bélanger & Fortier – Brochu	2006	Québec	Examination of the relationship among sleep, insomnia and psychopathology	/	/		Journal Article
Potvin, Lorrain, Belleville, Grenier & Préville	2014	Québec	Identify subjective sleep characteristics specific to anxiety and depression in a population	Random sample of individuals aged 65 years or older	N = 2393 N = 80 part. with AD		Analytic: Retrospective cohort study; descriptive: cross – sectional design; statistical analyses as logistic regression to determine sleep characteristics associated with each syndrome
Ramsawh, Stein, Belik, Jacobi & Sareen	2009	San Diego	Investigation of the relationship of specific anxiety disorders with sleep quality, and functional impairment in a community sample	German Health Survey; individuals aged 18 - 79	N = 4181 N = 56 part. with GAD		Descriptive: Cross – sectional design; statistical analyses as multiple linear and logistic regressions
Shanahan, Copeland, Angold, Bondy & Costello	2014	North Carolina	Test whether sleep problems co – occur with, precede and/or follow common psychiatric disorders during childhood and adolescence; clarify role of comorbidity; test for specificity of associations among sleep problems and psychiatric disorders	Great Smoky Mountains Study, children between 9 – 16 years	N = 1420		Analytic: Prospective cohort study with cross – sectional and longitudinal analyses
Simon	2010	North Chicago	Book chapter about the association of psychiatric disorders and disturbed sleep and circadian rhythms	/	/		Book chapter
Sullivan, Kovalenko, York, Prescott & Kendler	2003	Richmond	Twin studies about the correlation between fatigue and psychological processes (GAD)	Two large longitudinal twin studies (female – female, male – male and male – female twin pairs; all with interfering fatigue)	N = 7740		Descriptive: Cross – sectional statistical evaluation of the data from two longitudinal studies including twin pairs
Thielsch, Ehring, Nestler, Wolters, Kopel, Rist, Gerlach & Andor	2015	Münster	Assessment of bidirectional pathways of worry and associated phenomena in everyday life of GAD patients	GAD patients from a clinical intervention study in Münster; inclusion criteria GAD diagnosis and age 18 – 65	N = 56		Statistical analyses of participant's electronic log book of sleep quality and the results of the previously answered list of questionnaires processes 4 times/day
Tsypes, Aldao & Mennin	2013	New York	Examination of emotion dysregulation as a potential contributor to sleep problems in GAD patients	Participants recruited from an urban community in the northeast United States age 21 - 65	N = 59 GAD pat., N = 66 healthy contr.		Descriptive: Cross – sectional design

The included studies used a number of different measurement methods in order to assess anxiety and GAD, fatigue, sleep related factors, worry, depression, global functioning or other domains, indicating that there is not one generally accepted and applied way to measure those factors. Given the diversity of measurement methods, a good comparison of study outcomes can be impaired. Anxiety and GAD were assessed using (semi-) structured interviews as well as self – report questionnaires. Interestingly, only one study directly assessed fatigue. All of the other studies that were included in the current review measured sleep quality, which was assessed with various self – report questionnaires. Two studies categorized anxiety and sleep problems on DSM – IV or DSM – V criteria, without using standard measurement methods, one study analyzed the results of personal non standardized interviews by assessing multiple domains as physical status, psychiatric disorders, personality and stressful life events. Finally, there were five studies that included other measurement methods in order to measure personality structures, Mood States, Irritability, Depression, Global Assessment of Functioning, Medical Outcomes, Clinical Severity, Emotion Regulation and Metacognitions. Generally, it can be concluded, that those articles that used questionnaires or interviews mostly revert to more than one measurement method. An overview over the measurement methods of the included articles is presented in table five.

Table 5. *Measurement Methods of Included Studies*

<i>Authors</i>	<i>Measurement Methods</i>
Bélanger et al. (2004)	ADIS – IV by two individual blinded clinicians; ISI, WAQ
Ebben & Spielman (2008)	/
Fairholme & Manber (2014)	PSQI, MFI, Dysfunctional Beliefs and Attitudes about Sleep Scale, Sleep – Related Behaviors Questionnaire, Glasgow Sleep Effort Scale, Depression Anxiety Stress Scale, NEO FFI
Faravelli et al. (2012)	M.I.N.I., FPI
Herring et al. (2011)	Psychiatric Diagnostic Screening Questionnaire GAD; PSWQ; ADIS – IV; STAI – Trait, POMS – B, IRQ; BDI – II
Lijun et al. (2012)	SCID – IV – TR; PSQI, GAF
Marcks et al. (2010)	SCID – IV; Anxiety Screening questionnaire; SPRAS
Morin et al. (2006)	/
Potvin et al. (2014)	Cat. of anxiety and depression on the basis of DSM – V crit. GAD; PSQI
Ramsawh et al. (2009)	PSQI, DIA – X/M – CIDI; SF – 36
Shanahan et al. (2014)	Assessment for major Diagnostic and Statistical Manual – Fourth Edition (DSM – IV) disorders and sleep problems
Simon (2010)	/
Sullivan et al. (2003)	Analysis of the data of two longitudinal twin studies; data results pers. interviews assessing multiple domains: physical status, psychiatric disorders, personality, stressful life events
Thielsch et al. (2015)	SCID, PSWQ, MCQ; distinct question items on worry duration, worry frequency and worry uncontrollability; one – item concerning sleep quality: “How well did you sleep last night?”
Tsypes et al. (2013)	SCID, ADIS – IV, CSR, DERS, PSQI

- a. ADIS – IV: Anxiety Disorder Interview Schedule – IV
- b. BDI – II: Beck Depression Inventory – II
- c. CSR: Clinical Severity Rating
- d. DERS: Difficulties in Emotion Regulation Scale
- e. DIA – X/M – CIDI: Munich Composite International Diagnostic Interview
- f. FPI: Florence Psychiatric Interview
- g. GAF: Global Assessment of Functioning
- h. IRQ: Irritability Questionnaire
- i. ISI: Insomnia Severity Index
- j. M.I.N.I.: Mini International Neuropsychiatric Interview
- k. MCQ: Metacognitions Questionnaire
- l. MFI: Multidimensional Fatigue Inventory
- m. NEO – FFI: Neuroticism Extraversion Openness– Five Factor Inventory
- n. POMS – B: Profile of Mood States Brief form
- o. PSQI: Pittsburgh Sleep Quality Index
- p. PSWQ: Penn State Worry Questionnaire
- q. SCID – IV: Structured Clinical Interview for DSM – IV Disorders
- r. SF – 36: Medical Outcomes Scale Short Form
- s. SPRAS: Sheehan Patient Anxiety Scale
- t. STAI – Trait: State – Trait Anxiety Inventory
- u. WAQ: Worry and Anxiety Questionnaire

3.2 Etiology

The literature search on the relationship between GAD and fatigue showed that there are different ideas and theories on the development and etiology of GAD and fatigue. There is uncertainty about the question whether poor sleep and its consequences, amongst them fatigue, are a distinct disorder next to GAD or rather a result of GAD. Of the in the current review included articles were seven studies that yielded information on this sub question. All of them primarily assessed sleep difficulties or sleep quality, but were included because they proved that there was a close relationship between poor sleep and fatigue in GAD. The results are presented in table six. In total, eight different theories and hypotheses were addressed. In the following section all of them are shortly described and sorted by the corresponding authors.

3.2.1 Interrelationship between sleep and GAD

First of all, there is agreement over different authors who advocate for an interrelationship between poor sleep and anxiety and mood disorders in general, and GAD specifically. The current review includes the article of a group of American researchers who argue that sleep disturbances are more common in GAD patients, while referring to a high comorbidity of GAD with MDD, which is assumed to have a strong relation with sleep difficulties, too (Marcks et al., 2010). The authors also claim that MDD often develops after the onset of the anxiety disorder and that MDD in turn impacts the course of the anxiety disorder negatively (Marcks et al., 2010). Another group of American researchers recently provided evidence that poor sleep predicts and in turn is predicted by GAD (Shanahan et al., 2014), suggesting poor sleep to be a risk factor for GAD, and GAD being a risk factor for poor sleep. They furthermore suggested screening children for sleep problems in order to provide opportunities for reducing mental illnesses in the early life course (Shanahan et al., 2014). But there is another group of American authors on the other hand who found moderate evidence that insomnia is rather a result of GAD than a distinct disorder (Bélanger et al., 2004).

3.2.2 Spielman 3P model

Ebben and Spielman (2008) present the Spielman 3P model as an explanation for the onset and maintenance of insomnia in GAD patients. The authors use the term psychophysiological insomnia in order to describe insomnia that results from excessive worry that prevents sleep. The three P's in this model represent

predisposition, precipitation and perpetuation. Summarized, this model explains that individuals with a general high tendency for excessive rumination (predisposition) begin to have difficulties with sleeping because of a triggering event or an environmental factor that causes awakenings from sleep (precipitation). Insomnia is then maintained by factors as conditioned wakefulness or increased anxiety (perpetuation). The authors claim that GAD patients have a general greater risk for developing psychophysiological insomnia because of a general tendency for rumination and worry, which they call hyperarousal. This hyperarousal is therefore assumed to be a major underlying theme for anxiety and sleep disorders (Ebben & Spielman, 2008), whereas GAD is supposed to be a risk factor for insomnia (Ebben & Spielman, 2008). Hyperarousal is defined as “a combination of physiological, mental, and behavioral traits associated with arousal” (Ebben & Spielman, 2008, p. 224). The authors give examples of hyperarousal that include responsiveness to caffeine and bright lights, trouble falling asleep on daytime naps, elevated blood hormone levels, a strong startle reaction to loud noises, rumination or negative response to unexpected events (Ebben & Spielman, 2008). Moreover, these authors concluded, that insomniacs generally are less sleepy during the day than individuals without insomnia, indicating that they are hyperaroused.

3.2.3 Metacognitive model of worry

The metacognitive model of worry is presented by a group of German researchers (Thielsch et al., 2015). This recent research emphasizes the role of metacognitions concerning uncontrollability in the maintenance of worry. Patients' metacognitions on this uncontrollability lead to the assumption that maintenance of rumination is dangerous. The authors further replicate earlier results regarding a strong relationship between worry and sleep with worry leading to poorer sleep quality and vice versa (Thielsch et al., 2015), indicating a vicious circle. As by the author of the

current review self-designed version of this vicious circle is presented in figure two.

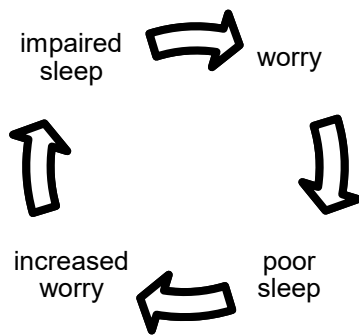


Figure 2. Vicious circle of poor sleep and worry, based on Thielsch et al. (2015)

3.2.4 Emotion dysregulation model of GAD

Tsypes, Aldao & Mennin (2013) present the emotion dysregulation model of GAD. They explain that emotion regulation difficulties, which are assumed to characterize GAD, also mediate the relationship between symptoms of GAD and sleep difficulties. The authors claim, that sleep interference has been shown to be caused by the tendency to worry before going to bed or while lying in bed (Tsypes et al., 2013). And GAD is, as is stated above, defined by excessive, uncontrollable and pervasive worry, assuming a special predisposition for GAD patients to worry before going to bed. Moreover, the authors explain that sleep deprivation is related to increases in negative affect and decreases in positive affect in both, clinical and healthy samples.

3.2.5 Other explanations

Another group of American researchers provides three different explanations on the development of fatigue in GAD (Ramsawh et al., 2009). First, those authors explain the vicious circle of anxiety and sleep, which equates the model of Thielsch et al. (2015), which was described in the section above. Ramsawh et al. (2009) conclude that poor sleep would increase the levels of anxiety, thereby leading to more symptoms, amongst them daytime dysfunction, which in turn negatively affect sleep. Daytime dysfunction is by the authors defined as daytime sleepiness and difficulty keeping up enough enthusiasm to get things done (Ramsawh et al., 2009). Especially GAD was in their study associated with daytime dysfunction, in comparison to other anxiety disorders (Ramsawh et al., 2009). They also conclude, that poor sleep and comorbid anxiety disorders were related to a greater likelihood of poor mental health – related quality of life, than anxiety disorders alone. Second, they

raise the question of whether poor sleep is only a marker for more severe anxiety disorders. Finally, they introduce the third variable hypothesis, meaning that a third, yet unknown variable might be responsible for the etiology of GAD and sleep (Ramsawh et al., 2009).

Table 6. *Etiology of GAD and Fatigue or Poor Sleep*

<i>Authors</i>	<i>Objective</i>	<i>Outcome</i>
Bèlanger et al. (2004)	Examination of the impact of treating GAD with CBT interventions on insomnia symptoms	Moderate evidence that insomnia is a result of GAD
Ebben & Spielman (2008)	Discussion of the relationship between sleep and quality of life in anxiety disorders	Spielman 3P model as explanation for insomnia onset and maintenance in anxiety; hyperarousal as underlying factor
Marcks et al. (2010)	Examination of the relationship between sleep disturbance and course of anxiety	Sleep disturbance is a risk factor for development and maintenance of anxiety disorder
Ramsawh et al. (2009)	Investigation of the relationship of specific anxiety disorders with sleep quality and functional impairment	Various explanations: a) vicious circle b) poor sleep is marker for severe anxiety c) third variable hypothesis
Shanahan et al. (2014)	Sleep problems predict and are predicted by diagnostic cluster including MDD, ODD and GAD	Sleep problems are risk factor for GAD; GAD risk factor for sleep problems
Thielsch et al. (2015)	Assessment of bidirectional pathways of worry and associated phenomena in life of GAD patients	Metacognitive model of worry; replication of earlier results regarding a bidirectional relationship between worry and sleep
Tsypes et al. (2013)	Examination of emotion dysregulation as a potential contributor to sleep problems in GAD patients	Emotion dysregulation model of GAD as explanation for close relationship between worry and sleep problems

In summary there are different approaches in finding an explanation for the strong relationship between GAD and fatigue by meaning of etiology. Some authors agree that poor sleep is a risk factor for anxiety; others propose the Spielman 3P model, the metacognitive model of worry or the emotion dysregulation model of GAD. Moreover, there are authors who claim for a vicious circle of poor sleep and anxiety symptoms, raise the idea of poor sleep being only a marker of more severe anxiety or introduce the third variable hypothesis.

3.3 Diagnosis

The literature search on the relation between fatigue and GAD showed that eleven of the included studies yielded information on the sub question whether fatigue is included in the diagnostic criteria. Of those eleven studies, eight presented information on poor sleep and GAD, two on fatigue and GAD and one evaluated diagnostic criteria of GAD in comparison to other psychiatric disorders. The results are presented in table seven.

3.3.1 Fatigue

The results on this sub question show, that fatigue and related symptoms as decreased vigilance, restlessness, low energy and poor concentration are commonly reported by patients, but not an essential criterion for this disorder (Bélanger et al., 2004; Ebben & Spielman, 2008; Faravelli et al., 2012; Herring et al., 2011; Marcks et al., 2010; Morin et al., 2006; Ramsawh et al., 2009; Sullivan et al., 2003; Tsypes et al., 2013). A twin study from 2003 found, that there is evidence that fatigue is more strongly associated with GAD in comparison to other psychopathology, given the high comorbidity of those (Sullivan et al., 2003).

3.3.2 Problem of poor specificity and comorbidity

Other researchers concluded that GAD as a disorder is, however, not related to a clear prototype and that there is still a poor specificity of GAD symptoms (Faravelli et al., 2012), suggesting a problem with a clear definition of GAD. It is therefore supposed that a proper diagnosis would lead to a better understanding of this disorder (Simon, 2010). Another problem with diagnosing GAD is associated with a high comorbidity of this disorder with mainly MDD, but also other anxiety disorders as panic disorder (PD) or social anxiety disorder (SAD) and even with sleep disorders (Ebben & Spielman, 2008; Faravelli et al., 2012; Herring et al., 2011; Marcks et al., 2010; Morin et al., 2006). Those psychiatric disorders are found to share symptoms, amongst them restlessness, difficulties concentrating, poor sleep, obsessive rumination, somatization and fatigue, suggesting some underlying mechanisms (Morin et al., 2006; Faravelli et al., 2012; Herring et al., 2011). However, the most cardinal features of GAD are still anxiety or worry – related symptoms (Bélanger et al., 2004; Faravelli et al., 2012).

3.3.3 Sleep disturbance

Next to fatigue, there are eight of the included studies that concentrate on sleep disturbance or insomnia complaints as symptoms of GAD. Their results, however, are somehow related to fatigue, too. Insomnia symptoms are also a common feature of GAD and reported by a significant number of GAD patients (Bélanger et al., 2004; Ebben & Spielman, 2008; Marcks et al., 2010; Morin et al., 2006; Lijun et al., 2012; Ramsawh et al., 2009; Simon, 2010; Tsypes et al., 2013), as well as MDD patients or patients with posttraumatic stress disorder (PTSD) (Ebben & Spielman, 2008; Marcks et al., 2010). The prevalence of sleep disturbances in GAD patients is estimated by a group of Chinese researchers, who found that about 58.27% of GAD patients report sleep disturbances, which was significant in comparison to a control group (Lijun et al., 2012). A group of American researchers reported similar results in 2010. They found that GAD patients, as well as PTSD patients, were two times more likely to have sleep problems in comparison to other primary care patients, and that GAD has the highest comorbidity rate with insomnia (Marcks et al., 2010). Those results were supported by the results of another group of American researchers who found in 2013 that sleep problems are twice more likely in GAD patients than in other anxiety disorders (Tsypes et al., 2013).

In conclusion one can state that fatigue, as well as sleep difficulties are more common among GAD patients than other psychopathology, and even belong to the diagnostic criteria, but that both concepts are not an essential criterion for the diagnosis. One frequently reported problem addresses the high comorbidity rate of GAD with, among others MDD, and the overlap of symptoms of those disorders.

Table 7. *Diagnosis of GAD and Fatigue or Poor Sleep*

<i>Authors</i>	<i>Objective</i>	<i>Outcome</i>
Bèlanger et al. (2004)	Examination of the impact of treating GAD with CBT interventions on insomnia symptoms	Sleep problems symptoms but not essential criterion for disorder; insomnia leads to fatigue complaints
Ebben & Spielman (2008)	Discussion of the relationship between sleep and quality of life in anxiety disorders	Insomnia common feature of GAD; high comorbidity of GAD and MDD
Faravelli et al. (2012)	Evaluation of coherence, psychopathological pattern, robustness of criteria and clinical utility of GAD	GAD overlap with other DSM – IV disorders; GAD symptoms frequent in other mood and anxiety disorders
Herring et al. (2011)	Comparison of effects of six weeks RET and AET on signs and symptoms of GAD	GAD patients report the following symptoms: restlessness, anxiety, fatigue, difficulty concentrating, irritability, muscle tension, pain and depression
Lijun et al. (2012)	Investigation of sleep characteristics of a community sample of patients with mental disorders	Prevalence of sleep disturbance in GAD about 58.27%; significant difference in sleep in subjects with and without GAD
Marcks et al. (2010)	Examination of the relationship between sleep disturbance and the course of anxiety disorders in primary care patients	GAD/PTSD patients more likely to have sleep problems; GAD highest comorbidity rate with insomnia; sleep disturbance included in diagnostic criteria, high comorbidity of GAD with MDD
Morin et al. (2006)	Examination of the relationship among sleep, insomnia and psychopathology	Insomnia as well as related symptoms as fatigue, low energy and poor concentration are among the diagnostic criteria of GAD
Ramsawh et al. (2009)	Investigation of the relationship of specific anxiety disorders with sleep quality and functional impairment	Sleep disturbance included in diagnostic criteria, although not requisite for diagnosis; sleeping problems and GAD related to daytime dysfunctioning
Simon (2010)	Book chapter about the association of psychiatric disorders and disturbed sleep and circadian rhythms	Sleep disturbance one of the most common complaints associated with psychiatric disorders; GAD has sleep disturbance in the criterion; proper diagnosis leads to better understanding of this disorder
Sullivan et al. (2003)	Twin studies about the correlation between fatigue and psychological processes	Interfering fatigue (IF) significantly associated with correlates; most strongly with GAD, MDD, health problems and neuroticism
Tsypes et al. (2013)	Examination of emotion dysregulation as a potential contributor to sleep problems in GAD patients	Relationship between GAD and sleep problems; sleep problems included in diagnostic criteria; two – times more likely in GAD in comparison to other anxiety disorders; highest comorbidity rate

3.4 Treatment

The literature search on the relationship between fatigue and GAD showed that fatigue is not included in the treatment of GAD per se. As is mentioned above, there is a high prevalence of poor sleep or sleep difficulties and fatigue. Most of the in the current research included studies investigated sleep specific factors in the treatment of GAD, instead of assessing fatigue directly. This can be due to the fact that those studies presented arguments for fatigue being a result of poor sleep and therefore put the focus on the quality of sleep. But, on the other hand, as Ebben and Spielman conclude in 2008, there is generally only little literature on the integration of sleep specific factors in the treatment of GAD. However, there are in total seven studies of the in the current research included articles, that present information on this sub question. The results are presented in table eight.

3.4.1 Cognitive behavioral therapy (CBT)

Of those seven studies, four analyzed CBT in GAD patients. CBT, or a combination of CBT with psychopharmacology, is assumed to be the most effective treatment for GAD in order to decrease anxiety related factors and increase the general quality of life (QoL) of GAD patients (Bélanger et al., 2004; Ebben & Spielman, 2008). The psychopharmacological treatment is found to only attenuate some of the various symptoms of GAD and even worsen the sleep related symptoms (Herring et al., 2011). But CBT on the other hand is assumed to be positively related to sleep quality. One group of American researchers found in an RCT that if the disorder is treated right, the sleep difficulties decrease and that especially CBT treatments that address worries instead of sleep specific topics lead to a significant decrease in insomnia symptoms (Bélanger et al., 2004). However, those authors also addressed the question of whether poor sleep is a coexisting condition or rather caused by this disorder. They then assumed that treating GAD with CBT would lead to improvements in sleep and found proof for this hypothesis. Another group of authors who investigated the relationship between GAD and sleep disturbance concluded also that CBT treatment of GAD alone would lead to improvements in sleep related factors and anxiety symptoms (Ebben & Spielman, 2008).

One commonly mentioned problem concerning the treatment of GAD patients was that poor sleep and fatigue often persist after successful treatment of the anxiety disorder. More recently than the above mentioned studies, it has been found that

sleep difficulties as well as dispositional mechanisms, like the ability to regulate emotions, remain persistent after improvement of GAD (Tsypes et al., 2013). The authors therefore concluded that CBT for anxiety disorders has only a moderate effect on co – occurring sleep difficulties and vice versa (Tsypes et al., 2013). They further suggested that GAD treatment should directly target emotion regulation strategies in order to reduce sleep problems. One year later, in 2014, another group of researchers who characterized subjective sleep complaints in various anxiety disorders assumed, that reducing symptoms of anxiety could lead to a reduction of poor sleep and the other way round (Potvin et al., 2014). Another group of Canadian researchers concluded earlier, in 2006, that treatment of patients with GAD and fatigue or sleep related symptoms should directly target both conditions, in order to optimize treatment effects (Morin et al., 2006). Those conclusions are supported by Fairholme and Manber who found that sleep specific factors might be important treatment targets among patients with anxiety and depressive disorders with disturbed sleep, too (Fairholme & Manber, 2014). Finally, there is support for this conclusion by Simon, who declared in 2010 in his book chapter, that a proper treatment, which emphasizes sleep and circadian rhythm, would lead to better treatment outcomes (Simon, 2010).

3.4.2 Exercise training

Another approved GAD treatment is a form of exercise training. Exercise training has been found to have positive effects on multiple symptoms of GAD, as poor concentration, depression, feelings of anxiety, muscle tension, pain and fatigue (Herring et al., 2011). Especially resistance exercise training (RET), which was in the referred study defined as low frequency lower – body weight lifting, has been found to result in larger improvements in symptoms of GAD, in comparison to aerobic exercise training (AET) (Herring et al., 2011). The above mentioned symptoms of GAD, amongst them fatigue, were found to improve in healthy adults as well (Herring et al., 2011).

3.4.3 Vicious circle of worry and sleep

Finally, there are German researchers who recently suggested on the basis of statistical evaluation of electronic log books of sleep quality of GAD patients, that in the treatment of GAD the aim should be to break the vicious circle of poor sleep which is affecting and promoting worry, and worry which is impairing sleep (Thielsch

et al. 15). They furthermore concluded that this should be the main aim in both, treating GAD and insomnia disorders.

Table 8. *Treatment of GAD and Fatigue or Poor Sleep*

<i>Authors</i>	<i>Objective</i>	<i>Outcome</i>
Bélanger et al. (2004)	Examination of the impact of treating GAD with CBT interventions on insomnia symptoms	CBT for GAD significant impact on sleep quality, even if sleep disturbances not specifically addressed in treatment
Ebben & Spielman (2008)	Discussion of the relationship between sleep and quality of life in anxiety disorders	Most effective treatment for GAD is CBT and psychopharmacology; treatment of sleep disorders alone has been shown to improve sleep and anxiety symptoms
Herring et al. (2011)	Comparison of effects of six weeks RET and AET on signs and symptoms of GAD	RET significantly reduces anxiety tension and frequency and intensity of irritability, trait anxiety, concentration, depression, pain, fatigue and vigor; AET improvements in trait anxiety, concentration, irritability, muscle tension, fatigue and vigor
Morin et al. (2006)	Examination of the relationship among sleep, insomnia and psychopathology	Treatment should directly target both co – existing conditions
Potvin et al. (2014)	Characterization of subjective specific sleep complaints related to each syndrome (anxiety and depression)	Reducing symptoms of anxiety could lead to a reduction of symptoms of insomnia and vice versa
Simon (2010)	Book chapter about the association of psychiatric disorders and disturbed sleep and circadian rhythms	Proper treatment with emphasis on sleep leads to better understanding of this disorder and improved outcome
Thielsch et al. (2015)	Assessment of bidirectional pathways of worry and associated phenomena in everyday life of GAD patients	Interventions should aim at breaking the vicious circle of sleep affecting worry and worry impairing sleep; these interventions needed in both, GAD and insomnia treatment
Tsypes et al. (2013)	Examination of emotion dysregulation as a potential contributor to sleep problems in GAD patients	Sleep difficulties in GAD persist after successful treatment; CBT for GAD moderate effect on co – occurring sleep difficulties and CBT for insomnia moderate effect on anxiety problems; GAD treatments should target emotion regulation to alleviate sleep problems

To summarize, it can be stated that the treatment of GAD does not generally include sleep and fatigue specific factors, even though there is reason to assume that an improvement in either the anxiety disorder, or the sleep difficulties may lead to an

improvement in the other. However, it is reported that sleep difficulties and fatigue often remain after successful treatment of GAD, which led some authors to the conclusion that adequate treatment should concentrate on both, anxiety and sleep related factors. Exercise treatment has been proven to be effective in enhancing both.

4. Discussion

4.1 Summary of Evidence

The main search results are in the following section discussed per sub question, addressing etiology of GAD and fatigue in the first paragraph, diagnosis of GAD in the second and treatment of GAD and fatigue in the third. The main results are then summarized and weighted with study characteristics and the strength of evidence for each study. Finally, the results are as far as is possible compared with and integrated in existing literature on anxiety and sleep difficulties or insomnia symptoms in order to form a distinct picture of the role of sleep in the relationship of GAD and serious fatigue complaints.

The current review could find eight different theories on the etiology of GAD that integrated fatigue. During the search it was striking that most of the studies that fit inclusion criteria primarily assessed sleep difficulties or insomnia symptoms, and dealt with fatigue as a result of poor and non-restorative sleep. This becomes obvious, amongst others, in the fact that only one of the included studies directly assessed fatigue, with help of the MFI. The problem of indirect measurement of fatigue will be discussed later in this section. Generally, in the discussion of the findings that belong to the etiology of GAD and the role of fatigue in this context, prospective cohort studies are weighted higher in relation to other studies, given that this is the favorable study design in assessing etiology. The first approach described an interrelationship between poor sleep and GAD. Different authors concluded that poor sleep is either the result of this anxiety disorder (Bélanger et al., 2004), or the other way round, namely that poor sleep is a risk factor for developing GAD (Marcks et al., 2010). Shanahan et al. (2014) lately concluded that sleep problems during childhood and adolescence co – occur with, predict and are predicted by different psychiatric disorders, amongst them GAD. Given the different study qualities, a good comparison of those studies is difficult, but, based on the good study quality of

Shanahan et al. (2014) it can be concluded that there is a form of interrelationship between both phenomena. This conclusion is supported by existing literature on sleep and anxiety in general, as it is stated in Gosling, Batterham and Christensen (2012) who found that ruminative style and somatic sensitivity predict sleep disturbance even after a period of four years. A Japanese study from the same year also concluded that rumination and worry were uniquely associated with a reduction in sleep quality and an increase in sleep disturbance (Takano, Iijima & Tanno, 2012). Rumination and worry, the most cardinal symptoms of GAD, can therefore be considered to be important factors in sleep, and, in the context of the current review, fatigue as a result of poor sleep, too. It can hence be assumed, that the close relationship between fatigue and GAD can be explained by the cardinal symptoms, given that they are supposed to be closely linked to, and even responsible for poor sleep. A group of German researchers continue with this idea by presenting the metacognitive model of worry, which emphasizes the role of metacognitions related to the uncontrollability and danger in the maintenance of worry (Thielsch et al., 2015). They directly ascribe worry to be leading to poor sleep which, on the other hand, would promote more worries. Even though this study was comprised of only 56 adult GAD patients, indicating a small sample size, the method of using electronic log book data of patients on the quality of sleep, and comparing them to a list of previously answered questionnaires, implies a close meshed monitoring of patients which is affecting the overall study quality beneficial. That metacognitions on worry are an important factor in GAD is known, given that the MCQ is one of the standard measurement methods to diagnose GAD (Emmelkamp et al., 2009). At that time, literature on metacognitions in etiology of GAD was poor, and there was only little empirical support. The results of Thielsch et al. (2015) can therefore serve as a supplement in that metacognitions also negatively impair sleep quality. Ebben and Spielman (2008) on the other hand refer to the Spielman 3P model as an explanation for onset and maintenance of insomnia in GAD. In this model they ascribe an important role to rumination, too, by claiming that a general tendency for rumination is a predisposing factor for insomnia in GAD patients. This tendency is by the authors referred to as hyperarousal. The authors conclude that hyperarousal is a common underlying factor in sleep and GAD (Ebben & Spielman, 2008). Their results are in accordance with general knowledge on GAD which is found to be associated and defined by an increased or dysregulated arousal system, as it is displayed in

Emmelkamp et al. (2009), Vandereycken et al. (2008) and Fricchione et al. (2004). Furthermore, there is support for the important role of arousal by existing literature on anxiety and insomnia, which could prove that arousal and worries are major factors in insomnia, too (Bélanger et al., 2004; Belleville, Cousineau, Levrier & St – Pierre – Delorme, 2011; Mason & Harvey, 2014; Tsypes et al., 2013). It can therefore be concluded that hyperarousal is likely to be critical in developing fatigue in GAD patients, too. Further and more actual research on the interaction between hyperarousal in sleep and GAD appears essential. Further research should also concentrate on investigating the relationship between MDD and hyperarousal, given the high comorbidity between depressive disorders and GAD. If hyperarousal was the important factor in fatigue in GAD patients, and given the fact that about half the patients also report symptoms of comorbid MDD, it appears interesting to investigate whether hyperarousal is the common underlying mechanism between those disorders. Another approach is the emotion dysregulation model of GAD, proposed by Tsypes, Aldao and Mennin in 2013. The authors concluded that difficulties with emotion regulation statistically mediated the relationship between sleep and GAD. Emotion regulation difficulties are assumed to characterize GAD patients, as is discussed in Emmelkamp et al. (2009), which leads the author of the current review to the assumption, that the close relationship between GAD and sleep can be explained by, amongst others, emotion dysregulation strategies, which are characteristic for GAD. Tsypes et al. (2013) further explain that worrying before going to bed, or while lying in bed, would promote sleep difficulties, leading to poor sleep and impaired daytime functioning. This is in accordance with the article of a group of American researchers who found that anxiety or related constructs as arousal, stress and worry are found to impair sleep in individuals trying to fall asleep or lying in bed in general (Belleville, Cousineau, Levrier & St – Pierre – Delorme, 2011). Finally, there are authors who underline the approach of a vicious circle of anxiety and sleep (Ramsawh et al., 2009), but given the poor quality of the study, this conclusion can mainly be weighted as a support for the conclusion by Thielsch et al. (2015). To sum up, it can be claimed that the relationship between GAD and fatigue needs further investigation with regard to etiology and development. The most concise problem was in connection with the terminology and composition of the studies, given that especially sleep and GAD were investigated instead of fatigue and GAD. However, there is a close relationship between poor sleep and fatigue and the included studies

referred to fatigue or daytime dysfunction instead. Generally, it can be concluded that a general tendency to ruminate or to worry are important in both, developing sleep difficulties, as well as developing GAD. Rumination, worry, metacognitions and hyperarousal can therefore be considered being responsible for poor sleep and GAD, leading to the experience of fatigue. Tsypes et al. (2013) concretize this idea by claiming that the tendency to worry before going to, or while lying in bed, would impair good sleep. The authors explain that merely lying in bed is the ideal place and opportunity to indulge in worrying. Being busy worrying would then prevent the person to fall asleep. There is still uncertainty about whether and how fatigue is responsible in the etiology of GAD, but based on the above mentioned findings, one could adopt the idea that rumination and worry, as well as hyperarousal are significantly involved.

The general conclusion with regard to the part of fatigue in the diagnosis of GAD can be that poor sleep and fatigue are common in GAD patients, and even more widespread in these patients in comparison to other psychopathology, but not an essential criterion for the diagnosis, even though they belong to the diagnostic criteria. The good study quality of the studies who investigated fatigue in GAD patients makes it valid to adopt that fatigue is a common feature of GAD patients. The literature search on fatigue and related concepts in GAD patients revealed that sleep disturbances in GAD patients are far more often investigated. There is common sense among authors who primarily examined sleep disturbances that those are common in GAD patients, and more common in comparison to other psychopathological disorders. Various studies with different study designs and diverse study qualities found proof for this result. Given the structure of the current review, and the fact that the focus is on fatigue instead of poor sleep, those studies are only considered as background knowledge. The fact that there are more studies available that assess sleep than studies that assess fatigue can be due to different reasons. First of all, one can relate to the above mentioned problem of an objective measurement of fatigue. As it is described in the introduction, there is uncertainty among authors and patients about how to diagnose and describe fatigue (Berrios, 1990; Finsterer & Mahjoub, 2014; Philips, 2015; Shen et al., 2006). There are, however, some measurement methods, that aim to assess fatigue and the most commonly used ones, provided by Shen et al. (2006), are summarized in table one.

But only one of those, namely the MFI, was used by one of the included studies (Fairholme & Manber, 2014), who were trying to investigate the maintenance of insomnia and fatigue in the context of anxiety disorders. That only one measurement questionnaire directly assessed fatigue could be due to various factors. For one it can be assumed that the above described measurement methods are not that public and commonly used in diagnosing fatigue as it was suggested by Shen et al. (2006), and that other measurement methods are more suitable. But a closer look on table five shows, that the MFI is in fact the only method that directly addresses fatigue, and that there were no other fatigue measurements, who have not been introduced by Shen et al. (2006). Secondly, it is possible that based on the fact that poor sleep is a risk factor for fatigue, the included studies chose to measure fatigue as an outcome of poor sleep as for example in the PSQI, which included a subscale that measures daytime fatigue. It is, based on the literature on fatigue, difficult to differentiate between fatigue as a result of sleep problems and fatigue as a result of psychopathology (Tkachenko et al., 2014) which impairs a good diagnosis. This could be reflected in the underrepresentation of fatigue measurement in the current study. A solution to this problem would include a study design that clearly distinguishes patients with sleep problems and fatigue, and patients with psychopathology, GAD, and fatigue, in order to compare those groups. Furthermore it is possible, that the different types of fatigue, as mentioned in the introduction, are present in different patient groups, and that GAD patients particularly suffer from chronic, pathological fatigue, which is described as abnormal, unusual or excessive and not relieved by resting (Shen et al., 2006). It is, on the other hand, just as likely to assume, that GAD patients suffer from acute or normal fatigue, given that the current review found evidence that fatigue in GAD can be explained by considerable sleep difficulties. Thirdly, it can be assumed that later studies referred to earlier published literature and chose to use the same measurement methods in order to make a good comparison more likely. However, at the moment the reason why fatigue was not assessed directly is not quite clear, and further research on fatigue and measurement appears essential.

One commonly reported problem concerning the diagnosis of GAD addresses comorbidity and the missing prototype. As a group of American researchers who investigated the coherence of GAD and the robustness of diagnostic criteria

concluded, there is no distinct prototype to GAD and the symptoms of GAD have a poor specificity (Faravelli et al., 2012). This research, having a good study quality, can be considered meaningful in that the experience of being a GAD patient can be very different for different patients and that fatigue may not be apparent in every GAD patient. The conclusion of this would be that there should be further investigation on which patients do experience fatigue and which do not. It is likely that there is a common underlying mechanism that would decide to whether a GAD patient suffers from fatigue or not. The second problem comprised comorbidity and was addressed by five groups of authors (Ebben & Spielman, 2008; Faravelli et al., 2012; Herring et al., 2011; Marcks et al., 2010; Morin et al., 2006). The highest comorbidity rate is between GAD and MDD, but also other anxiety disorders or sleep disorders are commonly comorbid. The problem with comorbidity is, that it may intensify the problems, leading to more complications, worse functioning, poorer mental health – related quality of life and generally a greater burden than each disorder alone (Belleville et al., 2011; Ebben & Spielman, 2008; Ramsawh et al., 2009): Furthermore, there are overlapping symptoms among the comorbid disorders, which makes it difficult to differentiate which symptom belongs to which disorder. Those overlapping symptoms between GAD and MDD are as summarized in the results section restlessness, difficulties concentrating, poor sleep, obsessive rumination, somatization and fatigue (Faravelli et al., 2012; Herring et al., 2011; Morin et al., 2006). This shows, that even in the overlapping symptoms, sleep and fatigue are listed both, suggesting a strong relationship between those, too. Given that especially GAD and MDD are commonly co – existing, and that fatigue is one of the diagnostic symptoms of MDD, too, it cannot be concluded precisely, that fatigue in patients with comorbidity really is a symptom of GAD. In the current review, the problem of comorbidity could not be excluded entirely, given that otherwise a significant number of studies had to be excluded, based on the fact that most studies did not exclude comorbidity themselves. Even though there were five studies that explicitly concentrated on GAD patients, this was not the case for all. The problem of comorbidity is in accordance with other existing literature on GAD, as it is addressed in the introduction. However, there is a growing need to investigate the relationship between GAD, comorbid MDD and fatigue, based on the current results.

The literature is somewhat mixed up with regard to treatment of GAD and associated fatigue. There are different treatment options but not one gold standard of treating GAD and fatigue, which is probably due to the fact that this relationship has not been investigated a lot and that there is furthermore not one generally accepted and used treatment for fatigue, except from the treatment options for CFS. The most supported and most mentioned treatment option is CBT, which has found to be well studied and effective (Bélanger et al., 2004; Belleville et al., 2004; Ebben & Spielman, 2008; Emmelkamp et al., 2009). There is evidence that CBT for GAD has especially positive effects on poor sleep symptoms, even if sleep specific factors were not directly addressed during treatment. Those results suggest that improving anxiety would automatically improve sleep quality, too. Even though the evidence for this hypothesis is only moderate, there is still indication that a form of CBT, whether or not including sleep specific factors or emotion regulation strategies, would improve sleep quality, which is in accordance with existing literature that proves that CBT is one of the most effective treatments for GAD, as well as CFS. Those results did however not present a good answer on the question whether and to what extent fatigue is included in CBT treatment for GAD. Another interesting approach was presented by a group of American researchers who advocate for exercise training in the treatment of GAD, arguing that exercise training would lead to significant improvements in, amongst others, fatigue. This is in accordance with existing literature on treating GAD, as it is summarized in Emmelkamp et al. (2009), who mentioned exercise training as a common method to treat GAD. The results of Herring et al. (2011) therefore underline the efficacy of exercise therapy and add the factor of improving fatigue as well, which is especially interesting in the context of the current review. Based on those findings, a combination of CBT and exercise training appears to be the best solution, in order to help patients reduce or handle rumination, which is supposed to be responsible for sleep difficulties. Breaking the vicious circle of poor sleep and worry should, as is declared by a group of German researchers, should be the main goal of GAD treatment (Thielsch et al., 2015). Therefore it can be assumed that including worry and rumination specific factors in the treatment of GAD is essential in reducing fatigue, based on the strong relationship of both, poor sleep and GAD with worry and rumination.

As it was reported in the results section, one commonly mentioned problem in treating GAD patients with fatigue is, that fatigue, as well as poor sleep, often persists after successful treatment of the anxiety disorder. This was striking, granted that there were several researchers who assumed reducing anxiety would also lead to a reduction in poor sleep and vice versa (Potvin et al., 2014). On the other hand, there were also a group of Canadian researchers who claimed that treatment should directly target both conditions (Morin et al., 2006) and Fairholme and Manber (2014) who recently concluded that sleep specific factors might be important treatment factors in patients with anxiety disorders. Simon (2010) summarizes this by claiming for a proper diagnosis and that an appropriate treatment, which emphasizes sleep, would lead to better treatment outcomes. Taking a look at the study quality, it becomes clear that these results should be taken carefully. Two of the included studies that gave an answer on this topic were a book chapter or journal article, one was a cross – sectional design with only 15 GAD patients and one was a retrospective cohort study with 80 participants, amongst them GAD patients, which indicates a broad variety of study designs. In summary this means the literature on this topic is still mixed up and needs further investigation. However, there is indeed a tendency to include sleep related factors in the treatment of GAD patients reporting fatigue.

4.2 Methodological Reflection and Theoretical Implications

There are a few limitations to the current review which are discussed in the following section.

4.2.1 Conceptualization of fatigue

First of all, there were difficulties with the concept of fatigue, as is mentioned in the introduction. Fatigue is a broad term with diverse types and variations and a pretty vague conceptualization, which is why there is still a broad lack of consensus on how to define fatigue. Given the common interchangeable use of fatigue and sleepiness by researchers as well as patients, it is difficult to distinguish these two concepts. Therefore the current review included different related concepts, as tiredness, sleepiness, exhaustion, vitality and lack of energy. Given the close relationship the search terms also included quality of sleep, in order to gain a broad spectrum of results. But the broad spectrum of search terms also means that even if these concepts share common experiences, there might still be differences in the

outcomes, which are not to be distinguished in the current research. It is likely, that different search terms were differently assessed in different contexts and would thus lead to other results, as it was discussed above. Despite these uncertainties, the current review still included the different concepts, given that variability is one of the characteristics of fatigue, and in order to form a distinct picture. One benefit of including different concepts is furthermore, that the probability to include all forms of fatigue rises. Different forms of fatigue, as are described by Shen et al. (2006) are not distinguished in the current study. This was based on the gained results, in which fatigue was not to be further explained. The author therefore could not recognize whether fatigue meant chronic versus acute, normal versus pathologic or psychological versus physical. Fatigue was thus considered a general term. Further research on different forms of fatigue in GAD patients appears essential and interesting.

4.2.2 Problem of comorbidity

Secondly, there is the problem of comorbidity. As mentioned above, there is a high comorbidity of GAD with, amongst others, MDD, sleep difficulties and other anxiety disorders. The current review did not exclude studies that did not explicitly exclude comorbidity, given that otherwise the total number of included studies would have decreased significantly. Apparently, there is not much literature about studies that examined GAD patients without a comorbid psychiatric disorder. It is likely, that this is due to the fact that up to 50% of GAD patients report comorbid depressive symptoms, which rigorously reduces the original population of GAD patients without comorbidity. This in addition to other comorbidity makes it very unlikely that one could gain an adequate sample size of GAD patients without comorbidity that still fit inclusion criteria. Moreover, based on the results of the current review, it is possible, that the problem is in the diagnosis of GAD. Since GAD symptoms show a great overlap with symptoms of MDD or anxiety disorders, it is probable, that a good diagnosis is in many cases difficult. The comorbidity makes it furthermore difficult to differentiate between symptoms of GAD and symptoms of the comorbid disorder. In the context of MDD and anxiety there is evidence that MDD often develops after the onset of an anxiety disorder and that it also negatively impairs the course of the anxiety disorder (Marcks et al., 2010). Until now it is unclear to what extent this is true for the relationship of GAD and MDD especially, but one could assume a similar

mechanism on the basis of the great number of shared symptoms. In that case the results of the current research could be biased in a way that the included studies presented a more close relationship between GAD and fatigue, whilst this relationship would actually be due to, or at least mediated by, the comorbid disorder. Further investigation on GAD and fatigue without comorbidity appears therefore essential.

4.2.3 Variety of studies

Thirdly, the current review included studies with various study designs, sample sizes, study populations, aims and locations. A broad variety of studies does on the one hand lead to a variety of studies, which could be beneficial in trying to present a broad picture, but on the other hand this makes it difficult to compare these studies. Comparing fifteen completely different studies impairs clear conclusions, given that the results had to be weighted on study quality. Therefore, the weighting was done by the author, based on recency, sample size, study design and study population, with more recent studies and greater sample sizes being more important, and studies including a population of GAD participants only being higher rated than studies including comorbidity, or anxiety disorders in general. With regard to study design were RCTs a superior methodology in assessing treatment options, longitudinal and cohort studies were superior in assessing etiology and cross – sectional designs superior in assessing diagnosis. The use of different measurement methods to assess fatigue, anxiety or poor sleep increases the difficulties that are related to a good comparison. As is mentioned above, there is not one common used method to assess fatigue and of the included studies, only one used one of the in the introduction in table one presented instruments. The quality of the current study could have been improved if fatigue was assessed directly, instead of indirect by assessing sleep. Furthermore, the location of the study was not very diverse. The bigger part of studies came from the United States of America, only one study was from Asia and three studies came from Europe. It is possible, that assessment methods, as well as etiology factors could be different across the continents, given that Asian people grow up in a collectivistic society, opposed to European people who grow up in more individualistic societies. Similarly it is conceivable that there are cultural differences between American and European patients. Those differences could become clear in way of daily life, attitude towards life as well as moral and ethical values, but also

with regard to environmental factors. Further research on this factor should clarify this fictional hypothesis. The sample size was divergent across studies, too. The smallest sample size was 30, the greatest 7740. Sample size alone does not form the study quality, but generally a greater sample size suggests better generalizability. Future research could be improved by including study design in the inclusion criteria.

4.2.4 Bias

Fourthly, there is the problem of possible bias. Different sorts of bias can be present in systematic reviews. Two sorts of bias are discussed in the following paragraph, namely study publication bias and selective reporting bias. Publication bias is bias with regard to what is likely to be published among what is available to be published, with a tendency of researchers to publish positive or significant outcomes more often in comparison to non – significant outcomes (Dwan, Altman, Arnaiz, Bloom, Chan, Cronin, Decullier, Easterbrook, Von Elm, Gamble, Gherzi, Ioannidis, Simes & Williamson, 2008). This sort of bias has recently received much attention, given that it has led to a significant bias of the published literature, making the available evidence unreliable. If the original literature is biased by the researchers, this would automatically lead to a bias of systematic reviews, which are based on what is published. Additional evidence suggests that there is a time lag bias, which is defined as the fact that research with no statistically significant outcomes takes longer to be published (Dwan et al., 2008), which could also affect systematic reviews who include a specific time interval of literature search. Publication bias is therefore especially important in evaluating the treatment section of the current study. RCTs are assumed to be the gold standard of study designs based on random assignment and control. However, there is still the likelihood of overestimating the effect of experimental treatments (Dwan et al., 2008). The current review cannot be cleared of publication bias, given that only published studies were to be included. Furthermore, only the published results were recorded. However, in the assessment of the results, it was tried by the researcher to weigh RCTs more than experimental trials without randomization. Unfortunately, no quality catalogue was used, which is why the estimation of study results might be susceptible for bias.

Selective reporting bias is a within – study bias, that is referred to as the selective reporting of outcomes from those originally measured within a study (Dwan et al., 2008). The selection can apply to individuals, groups or other data (Dwan et al.,

2008). As Dwan et al. (2008) conclude, there are two levels of which biases can affect systematic reviews, which are non – publication due to lack of significant or positive outcomes or a rejection of study reports on the one hand, and the selective non – reporting of outcomes within published studies on the basis of the results (Dwan et al., 2008). The current review avoided selective reporting bias by carefully reading the included articles and including all available information in clusters of information, which are described in tables five to nine.

4.3 Conclusion for Future Research

Based on the results of the current review and the discussion, a few conclusions for further research can be formulated. As it was expressed in the introduction and suggested by the results, there is a great social and individual burden associated with GAD and fatigue. Therefore it seems reasonable to claim for better screening and treatment methods. Especially assessing fatigue should be better standardized, based on the fact that only one study directly measured fatigue and there are various questionnaires that attempt to measure fatigue. Treatment of fatigue is, until now, not as developed as one might assume, given the high prevalence. As the results of the current review might suggest, there is room for improvement of treating fatigue in GAD, particularly because of the problem of persistence after treatment of GAD. Generally, there is a growing need for studies that compare GAD patients with a) GAD patients with comorbid MDD and b) MDD patients without comorbid GAD, in order to find out whether the comorbidity influences the results on etiology, diagnosis and treatment, and to investigate the relationship with fatigue. Furthermore, there should be further research on the role of hyperarousal in GAD patients, as it was suggested by the results on etiology. Finally, there is a need for an investigation of the role of fatigue in sleep disturbance and whether fatigue also occurs without sleep disturbance.

There are also a few suggestions for future systematic reviews on the relationship between GAD and fatigue. More strict inclusion criteria, which would exclude comorbidity or studies on sleep difficulties or insomnia, are assumed to present a clearer picture of the relationship between GAD and fatigue. Furthermore could a standardization of study design lead to a better comparison of study results.

4.4 Conclusion for Practice

Based on the results of the current review, it can be concluded, that physicians and therapists should be sensitive to fatigue in GAD patients. Including treatment of fatigue in the treatment of the anxiety disorders appears just as essential, as being sensitive to comorbidity. Moreover, a better investigation of the sort of fatigue could improve treatment, given that different sorts of fatigue also could react to different sorts of treatments. However, given the close relationship between fatigue and poor sleep, it can be assumed that a general inclusion of sleep hygiene in the standard treatment of GAD could not harm. Finally, GAD patients could be sensitive to fatigue related factors, too, especially given the problem of adequate report of this condition, as is mentioned in the introduction.

5. Conclusion

The relationship between GAD and fatigue is, although commonly reported, not investigated entirely. Until today, there is still uncertainty about of what kind this relationship is, to what extent fatigue does play a role in the development of GAD or the other way round, how fatigue is integrated in the diagnosis of GAD and whether it is included in the treatment for GAD. The current review aimed to present an answer to these questions. With regard to etiology, there are different approaches to explain the occurrence of fatigue and GAD. Generally, it can be concluded that a general tendency to ruminate or to worry is important in both, developing sleep difficulties, as well as developing GAD. Rumination, worry, metacognitions and hyperarousal can therefore be considered being responsible for poor sleep and GAD, leading to the experience of fatigue. With regard to diagnosis, there is common sense, that fatigue is a diagnostic criteria of GAD, but not essential in order to be diagnosed with it. The problem of comorbidity, especially with MDD, is addressed, indicating a great overlap of symptoms and suggesting a common underlying mechanism between both disorders. With regard to treatment, the conclusion was that fatigue is not generally included in the most promising treatment of GAD, which is assumed to be CBT, except for one study who investigated the effect of exercise training on fatigue. Worry and rumination, which are considered the cardinal symptoms of GAD, appear to have an important role in treating GAD, given that treatment which includes worry specific factors would also have a positive influence on sleep related factors. Problematic

was, that studies investigated poor sleep instead of fatigue, which could at most present indirect answers on the research questions. Further research on fatigue and GAD is indicated, given that there is no standardization of investigating fatigue. The study design could be improved by specifying the inclusion criteria, in order to improve the comparison of studies.

Acknowledgment

Hereby I would like to express my gratitude to my attendants Dr. Christina Bode and Dr. Peter Meulenbeek, for useful comments, remarks and engagement through the writing process of this master thesis. Furthermore I would like to thank my dear friend, Martin Schregel, as well as my family, for supporting me during the entire process, to keeping up my motivation and to stand my moods, even, and especially, in busy times.

References

Bates, D.W., Schmitt, W., Buchwald, D., Ware, N.C., Lee, J., Thoyer, E., Kornish, J. & Komaroff, A.L. (1993). Prevalence of Fatigue and Chronic Fatigue Syndrome in a Primary Care Practice. *JAMA International Medicine*, Volume 153, No. 24, pp. 2759 – 2765, DOI: 10.1001/archinte.1993.00410240067007

Bélanger, L., Morin, C.M., Langlois, F. & Ladouceur, R. (2004). Insomnia and generalized anxiety disorder: Effects of cognitive behavior therapy for gad on insomnia symptoms. *Journal of Anxiety Disorders*, Volume 18, Issue 4, pp. 561 – 571

Belleville, G., Cousineau, H., Levrier, K. & St – Pierre – Delorme, M.E. (2011). Meta – analytic review of the impact of cognitive – behavior therapy for insomnia on concomitant anxiety. *Clinical Psychology Review*, Volume 31, Issue 4, pp. 638 – 652, DOI: 10.1016/j.cpr.2011.02.004

Bennett, D.S., Ambrosini, P.J., Kudes, D., Metz, C. & Rabinovich, H. (2005). Gender differences in adolescent depression: Do symptoms differ for boys and girls? *Journal of Affective Disorders*, Volume 89, Issue 1 – 3, pp. 35 – 44, DOI: 10.1016/j.jad.2005.05.020

Berrios, G.E. (1990). Feelings of fatigue and psychopathology: A conceptual history. *Comprehensive Psychiatry*, Volume 31, Issue 2, pp. 140 – 151, DOI: 10.1016/0010-440X(90)90018-N

Dwan, K., Altman, D.G., Arnaiz, J.A., Bloom, J., Chan, A. – W., Cronin, E., Decullier, E., Easterbrook, P.J., Von Elm, E., Gamble, C., Gherzi, D., Ionnidis, J.P.A., Somes, J. & Williamson, P.R. (2008). Systematic Review of the Empirical Evidence of Study

Publication Bias and Outcome Reporting Bias. *PLoS ONE*, Volume 3, Issue 8, DOI: 10.1371/journal.pone.0003081

Demyttenaere, K., De Fruyt, J. & Stahl, S.M. (2005). The many faces of fatigue in major depressive disorder. *International journal of Neuropsychopharmacology*, Volume 8, Issue 1, pp. 93 – 105, DOI: 10.1017/S1461145704004729

Ebben, M.R., Spielman, A.J. (2008). Sleep and quality of life in anxiety disorders. *Sleep and Quality of Life in Clinical Medicine*, pp. 239 – 249, DOI: 10.1007/978-1-60327-343-5-26

Emmelkamp, P., Bouman, T. & Visser, S. (2009). *Angststoornissen en hypochondrie – diagnostiek en behandeling*. Houten: Bohn Stafleu van Loghum

Fairholme, C.P. & Manber, R. (2014). Safety behaviors and sleep effort predict sleep disturbance and fatigue in an outpatient sample with anxiety and depressive disorders. *Journal of Psychosomatic Research*, Volume 76, Issue 3, pp. 233 – 236, DOI: 10.1016/j.jpsychores.2014.01.001

Faravelli, C., Castellini, G., Benni, L., Brugnera, A., Landi, M., Lo Sauro, C., Rotella, F. & Ricca, V. (2012). Generalized anxiety disorder: is there any specific symptom? *Comprehensive Psychiatry*, Volume 53, Issue 8, pp. 1056 – 1062, DOI: 10.1016/j.comppsy.2012.04.002

Ferentinos, P.P., Kontaxakis, V., Havaki – Kontaxaki, B.J., Paparrigopoulos, T. & Dikeos, D. (2007). Sleep disturbances in relation to fatigue in major depression. *Journal of Psychosomatic Research*, Volume 66, Issue 1, pp. 37 - 42

Ferentinos, P.P., Kontaxakis, V.P., Havavi – Kontaxaki, B.J., Paplos, K.G. & Soldatos, C.R. (2007). The Measurement of Fatigue in Depression. *Psychopathology*, Volume 40, pp. 133 – 134, DOI: 10.1159/000098494

Ferguson, J.M. (2001). SSRI Antidepressant Medications: Adverse Effects and Tolerability. *The Primary Care Companion to the Journal of Clinical Psychiatry*. Volume 3, Issue 1, pp. 22 - 27

Finsterer, J. & Mahjoub, S.Z. (2014). Fatigue in Healthy and Diseased Individuals. *American Journal of Hospice and Palliative Medicine*, Volume 31, Issue 5, pp 562 – 575, DOI: 10.1177/1049909113494748

First, M.B. (2015). Structured Clinical Interview for the DSM (SCID). *The Encyclopedia of Clinical Psychology*, 1–6, DOI: 10.1002/9781118625392.wbecp351

Fricchione, G. (2004). Generalized Anxiety Disorder. *The New England Journal of Medicine*, Volume 351, pp. 675 – 682, DOI: 10.1056/NEJMcp022342

Gillin, J.C. (1998). Are sleep disturbances risk factors for anxiety, depressive and addictive disorders? *Acta Psychiatrica Scandinavica, Supplement*, Vol 98, Issue 393, pp. 39 – 43

Gosling, J.A., Batterham, P.J. & Christensen, H. (2012). Cognitive – behavioural factors that predict sleep disturbance 4 years later. *Journal of Psychosomatic Research*, Volume 73, Issue 6, pp. 424 – 429, DOI: 10.1016/j.jpsychores.2012.08.011

- Harvey, A.G. (2002). A cognitive model of insomnia. *Behaviour Research and Therapy*, Volume 40, Issue 8, pp. 869 – 893, DOI: 10.1016/S0005-7967(01)00061-4
- Herman, J. (2013). Psychiatric disorders and fatigue. *Sleep Medicine Clinics*, Volume 8, Issue 2, pp. 213 – 219, DOI: 10.1016/j.jsmc.2013.02.002
- Herring, M.P., Jacob, M.L., Suveg, C. & O'Connor, P.J. (2011). Effects of short – term exercise training on signs and symptoms of generalized anxiety disorder. *Mental Health and Physical Activity*. Volume 4, Issue 2, pp. 71 – 77, DOI:10.1016/j.mhpa.2011.07.002
- Knoop, H. & Bleijenberg, G. (2010). *Het chronisch vermoeidheids – syndroom: behandelprotocol cognitieve gedragstherapie voor CVS, eerste druk*. Houten: Bohn Stafleu van Loghum. ISBN: 9789031381944.
- Lijun, C., Ke – qing, L., Xiuli, S., Ze, C., Qinpu, J., Yanchao, H., Lianghui, G., Yang, Z., Jianfeng, L., Yongqiao, L., Laohu, Y. & Hua, L. (2012). A survey of sleep quality in patients with 13 types of mental disorders. *Primary Care Companion to the Journal of Clinical Psychiatry*, Volume 14, Issue 6, DOI: 10.4088/PCC.11m01173
- Marcks, B.A., Weisberg, R.B., Orlando Edelen, M. & Keller, M. B. (2010). The relationship between sleep disturbance and the course of anxiety disorders in primary care patients. *Psychiatric Research*, Volume 178, Issue 3, pp. 487 – 492, DOI: 10.1016/j.psychres.2009.07.004
- Mason, E.C. & Harvey, A.G. (2014). Insomnia before and after treatment for anxiety and depression. *Journal of Affective Disorders*, Volume 168, pp. 415 – 421, DOI: 10.1016/j.jad.2014.07.020
- Mattisson, C., Bogren, M., Horstmann, V., Tambs, K., Munk – Jørgensen, P. & Nettelbladt, P. (2007). Risk factors for depressive disorders in the Lundby cohort – A 50 year prospective clinical follow – up. *Journal of Affective Disorders*, Volume 113, Issue 3, pp. 203 – 215; DOI: 10.1016/j.jad.2008.07.002
- Meng, H., Hale, L. & Friedberg, F.(2011). Prevalence and Predictors of Fatigue Among Middle – Aged and Older Adults: Evidence from the Health and Retirement Study. *PMC US National Library of Medicine National Institutes of Health*. Volume 58, Issue 10; pp. 2033 – 2034, DOI: 10.1111/j.1532-5415.2010.03088.x
- Mennin, D.S, Heimberg, R.G., Turk, C.L. & Fresco, D.M. (2005). Preliminary evidence for an emotion dysregulation model of generalized anxiety disorder. *Behavior Research and Therapy*, Volume 43, pp. 1281 – 1310, DOI: 10.1016/j.brat.2004.08.008
- Morin, C. M., Bélanger, L. & Fortier-Brochu, É. (2006). Sommeil, insomnie et psychopathologie. / Sleep, insomnia, and psychopathology. *Canadian Psychology/Psychologie canadienne*, Volume 47, Issue 4, pp. 245-262. DOI: 10.1037/cp2006016
- Philips, R.O. (2015). A review of definitions of fatigue – And a step towards a whole definition. *Transportation Research Part F: Traffic Psychology and Behaviour*, Volume 29, pp 48 – 56, DOI: 10.1016/j.trf.2015.01.003

- Potvin, O., Lorrain, D., Belleville, G., Grenier, S. & Prévile, M. (2014). Subjective sleep characteristics associated with anxiety and depression in older adults: A population – based study. *International Journal of Geriatric Psychiatry*, Volume 29, Issue 12, pp. 1262 – 1270, DOI: 10.1002/gps.4106
- Ramsawh, H.J., Stein, M.B., Belik, S. – L., Jacobi, F. & Sareen, J. (2009). Relationship of anxiety disorders, sleep quality, and functional impairment in a community sample. *Journal of Psychiatric Research*, Volume 43, Issue 10, pp. 926 – 933, DOI: 10.1016/j.jpsychires.2009.01.009
- Shanahan, L., Copeland, W.E., Angold, A., Bondy, C.L. & Costello, E.J. (2014). Sleep problems predict and are predicted by generalized anxiety/depression and oppositional defiant disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, Volume 53, Issue 5, pp. 550 – 558, DOI:10.1016/j.jaac.2013.12.029
- Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Herqueta, 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. *Journal of Clinical Psychiatry*, Volume 59, pp. 22 - 33
- Shen, Jianhua, Barbera, J. & Shapiro, C.M. (2006). Distinguishing sleepiness and fatigue: focus on definition and measurement. *Sleep Medicine Reviews*, Volume 10, Issue 1, pp 63 – 76, DOI: 10.1016/j.smrv.2005.05.004
- Simon, E.K. (2010). Psychiatric Disorders Associated with Disturbed Sleep and Circadian Rhythms. *Encyclopedia of Neuroscience*, pp. 1167 – 1185, DOI: 10.1007/B978 – 008045046 – 9.01621 – 1
- Smets, E.M.A., Garssen, B., Bonke, B. & De Haes, J.C.J.M. (1995). The multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *Journal of Psychosomatic Research*, Volume 59, Issue 3, pp. 315 – 325, DOI: 10.1016/0022-3999(94)00125-O
- Sullivan, P.F., Kovalenko, P., York, T.P., Prescott, C.A. & Kendler, K.S. (2003). Fatigue in a community sample of twins. *Psychological Medicine*, Volume 33, Issue 2, pp 263 – 281, DOI: 10.1017/S0033291702007031
- Takano, K., Iijima, Y. & Tanno, Y. (2012). Repetitive Thought and Self – Reported Sleep Disturbance. *Behavior Therapy*, Volume 43, Issue 4, pp. 779 – 789, DOI: 10.1016/j.beth.2012.04.002
- Thielsch, C., Ehring, T., Nestler. S., Wolters, J., Kopel, I., Rist, F., Gerlach, A.L. & Andor, T. (2015). Metacognitions, worry and sleep in everyday life: Studying bidirectional pathways using Ecological Momentary Assessment in GAD patients. *Journal of Anxiety Disorders*, Volume 33, pp. 53 – 61, DOI: 10.1016/j.janxdis.2015.04.007
- Tkachenko, O., Olson, E.A., Weber, M., Preer, L.A., Gogel, H. & Kilgore, W.D.S., (2014). Sleep difficulties are associated with increased symptoms of psychopathology. *Experimental Brain Research*, Vol 232, Issue 5, pp. 1567 – 1574, DOI: 10.1007/s00221-014-3827-y

Tsai, S.C. & Lee – Chiong, Jr. T. (2013). Sleep disorders and fatigue. *Sleep Medicine Clinics*, Vol 8, Issue 2, pp 235 – 239, DOI: 10.1016/j.jsmc.2013.02.003

Tsypes, A., Aldao, A. & Mennin, D.S. (2013). Emotion dysregulation and sleep difficulties in generalized anxiety disorder. *Journal of Anxiety Disorders*, Volume 27, Issue 2, pp. 197 – 203, DOI: 10.1016/j.janxdis.2013.01.008

Vandereycken, W., Hoogduin, C.A.L. & Emmelkamp, P.M.G. (2008). *Handboek psychopathologie – deel 1 basisbegrippen*. Vierde, herziene druk. Houten: Bohn Stafleu van Loghum